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Palladium (II) Catalyzed Oxidation, Isomerization and Exchange of Olefins Allylic Alcohols and Allylic Ethers in Water and Methanol Solvents

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by

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The kinetics of the palladium(II)-catalyzed exchange of 2-methyl-d_3-4-methyl-3-penten-2-ol with methanol and its isomerization into the methyl ether of its allylic isomer, 2-methyl-4-methyl-d_3-2-methoxy-3-pentene, were studied. Under all conditions the rates of exchange and isomerization were the same. No oxidation was observed with this species. At $[Cl^-] \leq 1.2$ M the rate expression is: Rate = $k[PdCl_4^{2-}][\text{allyl alcohol}]/[H^+][Cl^-]^2$. At $[Cl^-] \geq 1.5$ M the rate expression is: Rate = $k[PdCl_4^{2-}][\text{allyl alcohol}]/[Cl^-]$. Both allyl alcohol and 4-methyl-3-penten-2-ol gave 3-methoxypropanal and 4-methyl-4-methoxy-2-pentanone respectively at low chloride. At high chloride, both gave exchange but no oxidation products, 3-methoxy-1-propene from allyl alcohol, and 4-methyl-4-methoxy-2-pentene and 2-methyl-4-methoxy-2-pentene from 4-methyl-3-penten-ol. The exchange of 2-ethoxy-2,4-dimethyl-3-pentene with methanol at low $[Cl^-]$ gave the expression: Rate = $k[PdCl_4^{2-}][\text{allyl ether}]/[H^+][Cl^-]^2$.

The kinetics of the palladium(II)-catalyzed exchange and isomerization of 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol in water were also studied. Under all conditions the rate of isomerization was the same as the rate of exchange. No oxidation was observed with this substrate. With $PdCl_4^{2-}$ catalyst at $[Cl^-] \leq 1.0$ M the rate expression is: Rate = $k[PdCl_4^{2-}][\text{allyl alcohol}]/[H^+][Cl^-]^2$. At $[Cl^-] \geq 2.0$ M the rate expression is: Rate = $k[PdCl_4^{2-}][\text{allyl alcohol}]/[Cl^-]$. With $PdCl_3Py^-$ catalyst at $[Cl^-] \leq 1.0$ M, the rate expression is: Rate = $k[PdCl_3Py^-][\text{allyl alcohol}]/[Cl^-]$.

Lastly the stereochemistry of the oxypalladation step of the oxidation of 2-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol was investigated using 1,3-chirality transfer. At $[Cl^-] \leq 0.80$ M the oxidation of this substrate by $PdCl_4^{2-}$ was found to have the rate expression: Rate = $k[PdCl_4^{2-}][\text{allyl alcohol}]/[H^+][Cl^-]^2$. Starting with 100 % ee (-)-(R)-(E)-2-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol, the oxidation product obtained was of the inverse configuration, (+)-(S)-4-hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone. Similar results were obtained for the (-)-(S)-(E)-starting alcohol. At higher $[Cl^-]$ no oxidation was observed and only the isomerization product, 2-methyl-1,1,1,5,5,5-hexafluoro-2-penten-4-ol, was detected in small quantities. Similarly the stereochemistry of the oxypalladation step in the isomerization of 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol was investigated. At $[Cl^-]$ = 0.1 M an inversion of configuration was observed during isomerization to 2-methyl-4-methyl-d_3-1,1,1,5,5,5-hexafluoro-3-penten-2-ol, and the % isomerization was equal to the % inversion. The opposite was observed at higher concentrations of chloride where only retention is seen. With $PdCl_3Py^-$ catalyst an inversion of configuration was obtained at $[Cl^-]$ = 0.05 M for the isomerization studies. The % isomerization was greater than the % inversion. At $[Cl^-]$ = 0.2 M only a retention of configuration was obtained, with the formation of the opposite geometric isomer. With $PdCl_3Py^-$ as catalyst, a K_1 of 20.3 was obtained for the oxidation of ethylene. The rate expression for oxidation was: Rate = $k[PdCl_3Py^-][\text{olefin}]/[Cl^-]^2[H^+]$. Oxidation was observed only at $[Cl^-] \leq 0.2$ M. In the absence of $CuCl_2$ and at 0.2 M chloride, only oxidation of ethylene to acetaldehyde was obtained. As $CuCl_2$ was added and the concentration increased past 4.0 M 2-chloroethanol was concurrently formed with acetaldehyde. The percentage of 2-chloroethanol formed increased with increase in $CuCl_2$ concentration.

The kinetics of the palladium(II)-catalyzed exchange of 2-methyl-d_3-4-methyl-3-penten-2-ol with methanol and its isomerization into the methyl ether of its allylic isomer, 2-methyl-4-methyl-d_3-2-methoxy-3-pentene, were studied. Under all conditions the rates of exchange and isomerization were the same. No oxidation was observed with this species. At $[Cl^-] \leq 1.2$ M the rate expression is: Rate = $k[PdCl_4^{2-}][\text{allyl alcohol}]/[H^+][Cl^-]^2$. At $[Cl^-] \geq 1.5$ M the rate expression is: Rate = $k[PdCl_4^{2-}][\text{allyl alcohol}]/[Cl^-]$. Both allyl alcohol and 4-methyl-3-penten-2-ol gave 3-methoxypropanal and 4-methyl-4-methoxy-2-pentanone respectively at low chloride. At high chloride, both gave exchange but no oxidation products, 3-methoxy-1-propene from allyl alcohol, and 4-methyl-4-methoxy-2-pentene and 2-methyl-4-methoxy-2-pentene from 4-methyl-3-penten-ol. The exchange of 2-ethoxy-2,4-dimethyl-3-pentene with methanol at low $[Cl^-]$ gave the expression: Rate = $k[PdCl_4^{2-}][\text{allyl ether}]/[H^+][Cl^-]^2$.

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product obtained was of the inverse configuration, (+)-(S)-4-hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone. Similar results were obtained for the (-)-(S)-(E)-starting alcohol. At higher [Cl^-] no oxidation was observed and only the isomerization product, 2-methyl-1,1,1,5,5,5-hexafluoro-2-penten-4-ol, was detected in small quantities. Similarly the stereochemistry of the oxypalladation step in the isomerization of 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol was investigated. At [Cl^-] = 0.1 M an inversion of configuration was observed during isomerization to 2-methyl-4-methyl-d_3-1,1,1,5,5,5-hexafluoro-3-penten-2-ol, and the % isomerization was equal to the % inversion. The opposite was observed at higher concentrations of chloride where only retention is seen. With $PdCl_3Py^-$catalyst an inversion of configuration was obtained at [Cl^-] = 0.05 M for the isomerization studies. The % isomerization was greater than the % inversion. At [Cl^-] = 0.2 M only a retention of configuration was obtained, with the formation of the opposite geometric isomer. With $PdCl_3Py^-$ as catalyst, a K_1 of 20.3 was obtained for the oxidation of ethylene. The rate expression for oxidation was: Rate = k[$PdCl_3Py^-$][olefin]/[Cl^-]^2[H^+]. Oxidation was observed only at [Cl^-] $\leq$ 0.2 M. In the absence of $CuCl_2$ and at 0.2 M chloride, only oxidation of ethylene to acetaldehyde was obtained. As $CuCl_2$ was added and the concentration increased past 4.0 M 2-chloroethanol was concurrently formed with acetaldehyde. The percentage of 2-chloroethanol formed increased with increase in $CuCl_2$ concentration.

This Dissertation is dedicated to my loving wife Ouida, and to our first child Richard, who has brought inspiration to our lives.

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CHAPTER I

INTRODUCTION

A. The Inorganic Chemistry of Palladium

Palladium was discovered in 1803 by W. H. Wollaston when he was investigating the refining of platinum.[1] He named it after the asteroid Pallas which was newly discovered at the time. Palladium occurs in association with platinum, and is a rare element occupying only one in 10^{13} parts of the earth's crust. It is mined and purified mainly in Canada, South America and the U.S.S.R. There are several methods for its purification by various companies, most of which are held in patent. However Hartley has successfully outlined a general procedure for the extraction process from copper/nickel ores.[2,3]

Palladium metal has a grey-white lustre, and is fairly ductile and malleable. It can be easily drawn into a wire, or rolled into a sheet. This metal is resistant to corrosion and has a high melting point. The physical properties compared with those of platinum are summarized in Table I.1.[3]

When dispersed on a porous solid, palladium is a useful heterogeneous catalyst, an example is the ability to promote liquid-phase hydrogenation reactions in the general chemical, dyes and pharmaceutical industries. However, the focus this thesis will be on its properties and uses in homogeneous catalysis. The atomic weight of

Table I.1. Physical properties of palladium and platinum.

Property	Platinum	Palladium
Atomic number	78	46
Atomic weight (related to $^{12}C = 12$)	195.09	106.04
Density (g/cc at 20°C)	21.45	12.02
Crystal lattice	Face centered cubic	Face centered cubic
Lattice cell (Å)	3.1958	3.8825
Atomic radius (Å)	1.387	1.375
Allotropic forms	none known	none known
Melting point (°C)	1773.5	1554
Boiling point (°C estimated)	4530	3980
Thermal conductivity (cal/min/cm^2/sec/°C)	0.17	0.17
Linear thermal coefficient of expansion at 0°C (per °C)	8.9×10^{-6}	11.67×10^{-6}
Specific heat at 0°C (cal/g/°C)	1.0314	0.0584
Electrical resistivity at 20°C (micro-ohm-cm)	10.6	10.8
Hardness (annealed-Brinell Hardness number)	42	46
Tensile strength (annealed-ton/in^2)	9	13.8
Young's modulus (annealed-ton/in^2)	1.1×10^4	$8\text{-}8.8 \times 10^3$

palladium is 106.4 and its atomic number is 46. This places it in the group VIII elements, specifically in the subgroup known as the nickel triad, (Ni, Pd, Pt). Its outermost electronic configuration in the zero valency state is d^{10}. There are six known naturally occurring isotopes, ^{102}Pd (0.96%), ^{104}Pd (10.97%), ^{105}Pd (22.23%), ^{106}Pd (27.33%), ^{108}Pd (26.71%), ^{110}Pd (11.81%).

The inorganic chemistry of palladium is similar to that of platinum. Except for the free metal their radii are similar for different oxidation states. This similarity, which is quite common among pairs of second and third row transition metals, arises from the contraction of the atomic radius due to the imperfect shielding of outer electrons from the nuclear charge by the intermediately placed 4f electrons of the lanthanide series.[6,7,8,9,10,11,12] Also, on the Pauling electronegativity scale palladium and platinum have identical electronegativities. As a result there are

considerable similarities in the properties of these two metals.

This is reflected notably in their stable oxidation states. "Oxidation state" is defined as the formal charge left on the metal atom in their closed shell configurations, after all the ligands have been removed. There are four stable oxidation states of palladium and platinum, namely (0), (I), (II), and (IV). Of these the +1 oxidation state is very rare.

Palladium(0). The properties of the palladium(0) compounds are different from those of the crystalline metal itself. These compounds are in effect a way of keeping palladium(0) in a monomeric atomic and thus reactive form. They are very labile and easily oxidized, usually to the (II) state.

The zero oxidation state is stabilized by certain types of ligands called π-acid ligands.[13] This name, π-acid ligands, is given to these class of ligands because of their ability to accept electron density from the metal. CO is one of the most common π-acid ligands known. A large number of zero valent transition metal carbonyls are known. The general bonding picture for these carbonyls reflects the nature of the reactivity of the metal center and its readiness to give up electrons to become oxidized.

In the zero oxidation state palladium has its full compliment of electrons. Thus any addition of extra electrons by a Lewis base ligand will not be accepted unless there is some mechanism for removing the excess negative charge on the metal. For this reason simple Lewis bases such as ammonia and water will not form stable zero oxidation state complexes. The mechanism by which CO is able to bond with palladium(0)[59] is pictorially presented in Figure I.1. The back donation of electron density occurs by way of a filled metal orbital and an empty π^* orbital of the ligand. This type of interaction is presumed to also occur with other ligands such as isonitrile and bipyridyl. With trivalent ligands such as P, As, and Sb, Figure I.2

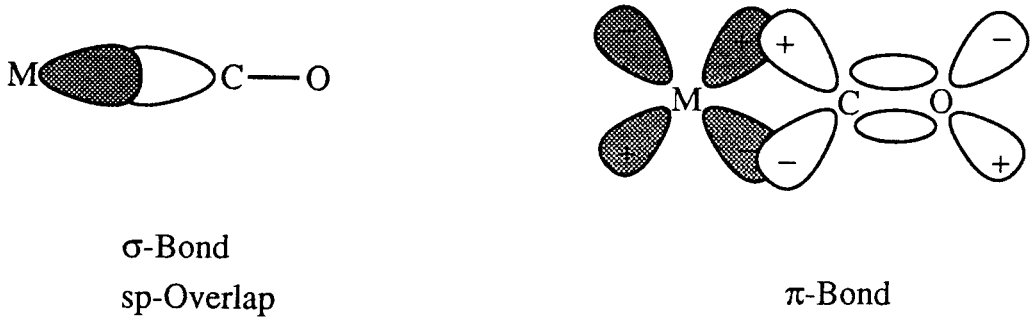


Figure I.1. Pictorial representation of metal-ligand π bonding for a ligand with vacant π^* orbitals, such as CO and bipy which can overlap with the metal d_{xz} orbital.

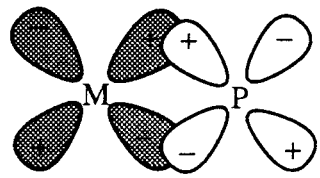


Figure I.2. Pictorial representation of metal-ligand π bonding for a *t*-phosphine or phosphite with a vacant d orbital on the phosphorus overlapping with the metal d_{xz} orbital.

remains analogous. These ligand have empty *d*-orbitals of proper symmetry and energy to overlap with the filled metal σ-orbital. This general type of bonding is termed synergistic because of the strengthening nature of the two effects. Thus a σ-bond is formed by the donation of electron density from the σ-orbital of the ligand L to an empty σ-orbital on the metal, and a π-bond formed by the back donation of electrons from filled π-orbitals of the metal to the appropriate empty orbitals of the ligand. This is simply represented as M⇄L .

There are several established methods for preparing palladium(0) complexes. Phosphines are usually prepared by either the direct reaction of the metal with the ligand,[14] or by the reduction of a palladium(II) compound in the presence of a π-acid ligand.[15] The cyano and isonitrile complexes are also prepared by the reduction of palladium(II) compounds.[16] The zero oxidation state is very important in palladium

catalysis, as it is usually involved in the cycling of the catalyst between two oxidation states, (0) and (II), as is usually a necessity in transition metal catalysis. Palladium(0) undergoes oxidative addition readily with a large number of reagents to form palladium(II) complexes. This property is effectively applied in palladium catalysis.

Palladium(I). In the nickel triad the +1 oxidation state has been clearly defined for nickel. However for platinum and palladium little is known about this oxidation state. It is well established that some organo-palladium species may initially decompose to give unstable univalent palladium.[17] Palladium(I) was first discovered in 1942 by Gel'man and Meilakh, as the carbonyl anion, $[PdCl_2CO]^-$.[18] A brief history of the development of the chemistry of this oxidation state is described by Hartley[3] and Henry.[19] In its +1 oxidation state palladium is in a d^9 electronic state. Its chemistry, as previously stated is not well known, but when compared to the zero oxidation states of Co, Rh, and Ir, and also the +2 oxidation states of Cu, Ag, and Au, which are also d^9 in character, similar behaviors are predictable for the entire nickel triad in the +1 oxidation state.[20] Mononuclear complexes of palladium or platinum in the +1 oxidation state have not been reported. They do have a tendency to form diamagnetic complexes with a M-M bond. These complexes and their structures have been studied by several groups. $[(C_6H_6Pd)_2(Al_2Cl_7)_2]$ and $[(C_6H_6Pd)_2(AlCl_4)_2]$ are two known complexes of this nature.[21] In spite of the labile nature of this oxidation state, progress in the synthesis, isolation and characterization of palladium(I) complexes is being reported.[22,23]

Palladium(II). The most common oxidation state for palladium is +2, where it readily acts as an oxidant. The redox potential for the couple: Pd(0)/Pd(II) is +0.92 volts in aqueous perchloric acid,[24] and +0.59, +0.49, and +0.18 volts in aqueous chloride, bromide and iodide solutions respectively.[25] This order of redox potentials

is related to the fact that palladium(II) is a soft acid as described by Pearson in the hard and soft acid-base theory,[26] so palladium(II) will complex more strongly with polarizable or soft ligands. The stability of halide complexes follows the order I^- >Br^->Cl^->>>F^-, which accounts for the order of redox potentials. Palladium(II) will also complex with other soft inorganic ligands such as phosphines, arsines, and stilbines, and soft organic ligands such as carbon monoxide, olefins and acetylenes. Much of its catalytic chemistry is related to its ability to coordinate unsaturated organic ligands.

Palladium(II) is a d^8 ion which prefers to form four coordinate square planar complexes. These complexes are diamagnetic as predicted from crystal field splitting diagrams.[13] Five coordinated complexes with π-acceptor type ligands are known. Their stereochemistries can be either trigonal bipyramidal, square pyramidal, or distorted square pyramidal.[27] A few octahedral complexes are known, the simplest being palladium(II) fluoride.[28] As would be predicted from orbital splitting diagrams the octahedral complexes are paramagnetic.[29]

Palladium(II) chloride is the most common and widely used palladium(II) halide salt. There are several patented methods of preparing this salt.[30] For instance, it can be prepared by the reaction of the metal with chlorine at 300°C. Palladium(II) chloride exists in α- and β- forms. The α- form is unstable, and consists of a linear chain of doubly chloride-bridged palladium(II)'s.[31] The β-form, which is more stable, consists of octahedral clusters of six palladium atoms which are joined by chloride bridges.[32] Salts of $PdCl_4^{2-}$, and $Pd_2Cl_6^{2-}$ have been prepared.[30,33,34]

In aqueous solution, studies of the polarographic and reduction behaviors of palladium(II) with complexing agents reveal the general trend with the following ligands:[35] CN^- > NH_3 > $NH_2CH_2CH_2NH_2$ ~ CH_3NH_2 > β-picoline ~ α-picoline > $C_2O_4^{2-}$ ~ NO_2^- > SCN^- > Br^- > Cl^-. Most important for the purpose of this thesis

are equilibria between palladium(II) and chloride ligand (equations I.1 to I.4). The

$$Pd^{2+} + Cl^- \rightleftharpoons PdCl^+ \quad K_1 \qquad (I.1)$$

$$PdCl^+ + Cl^- \rightleftharpoons PdCl_2 \quad K_2 \qquad (I.2)$$

$$PdCl_2 + Cl^- \rightleftharpoons PdCl_3^- \quad K_3 \qquad (I.3)$$

$$PdCl_3^- + Cl^- \rightleftharpoons PdCl_4^{2-} \quad K_4 \qquad (I.4)$$

equilibria have been studied by various groups who found the values of log β_4 ($\beta_4 = K_1K_2K_3K_4$), to be between 11 and 12 at 25 °C.[36] In other solvents with a lower dielectric constant palladium(II) tends to exist as a chloride bridged dimer.[37] At very low chloride conditions several dimeric species were reported.[38] Other ligands such as SCN^-[39] and CN^-[40] have been investigated although not as extensively as the halide ligands.

Methanol is often used as a solvent for the catalytic reactions of palladium. It has a dielectric constant of 32.63, between that of water, (78.36) and acetic acid, (6.15) at 25 °C.[41] Tetrachloro palladate(II) was found to have an equilibrium in methanol involving a solvated species,[42] at [LiCl] = 0.002 M, as shown in equation I.5. K_H has a value of 1.0×10^{-2} L mol^{-1} at 25 °C.

$$PdCl_4^{2-} + CH_3OH \overset{K_H}{\rightleftharpoons} PdCl_3(CH_3OH)^- + Cl^- \qquad (I.5)$$

In acetic acid it has been found that the following equilibrium (equation I.6),

$$Li_2Pd_2Cl_6 + 2LiCl \overset{K_{21}}{\rightleftharpoons} 2Li_2PdCl_4 \qquad (I.6)$$

exists between palladium(II) and chloride ligand in the presence of LiCl. The only

two species found were the dimer and monomer with the dimer as the major species.[43] At 25 °C the value of K_{21} was found to be 0.10 L mol^{-1}. Tetrachloropalladate(II) exists both as a monomer and dimer in acetic acid because of the very low dielectric constant for the acetic acid, 6.13 at 20°C.[44,45] Palladium(II) acetate in chloride-free acetic acid is a very important catalyst and exists as a trimer[46] in acetic acid.

In acetonitrile[47] and other less polar solvents very little work has been achieved, but there are indications that palladium(II) chloride exists as $Pd_2Cl_6^{2-}$.

Palladium(IV). This oxidation state plays a less important role in palladium chemistry. The ion has a d^6 valence electronic configuration, and thus is similar to the +3 oxidation states of Co, Rh, and Ir. It is diamagnetic and has a low spin octahedral geometry. Platinum(IV) has a lower reduction potential than palladium(IV).[25,48] There are a number of stable palladium(IV) complexes known. Of these the most studied is the binary halide PdF_4,[49] and the complex halides PdX_6^{2-}, where X = F, Cl, and Br.[49b] A few other salts of amines, nitrates, and some mixed valent complexes have been studied. Much work has been carried out on platinumt(IV) and cobalt(III) which are found to undergo substitution reactions very slowly, and are kinetically inert. Trends developed in the cobalt triad are predictable for the nickel triad, although very little has been done on this system, especially that of palladium(IV).

B. Palladium Catalysis

Homogeneous catalysis by transition metal complexes is one of the more important areas of organic synthesis and industrial chemistry today. Most of the interest stems from its industrial application to large scale commercial synthesis of organic chemicals. In the early growth of this field, most investigations were

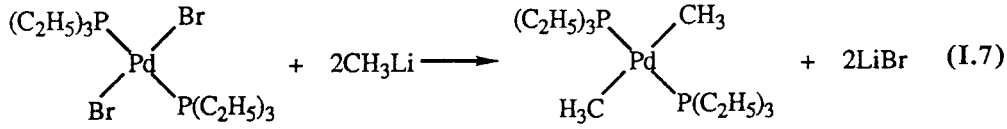
concerned with the preparative aspects of homogeneous catalysis. Much attention have been given to the mechanistic aspects of such systems, and a fair understanding of the reactions of homogeneous catalysis, including oxidative addition[50] and insertion[51] reactions have been achieved.

Because of commercial interest, homogeneous catalysis by palladium(II) is the most widely studied of all homogeneous catalytic systems. There are numerous books and reviews on the various aspects of catalytic palladium chemistry, the most comprehensive of which are the books written by Maitlis,[4] Hartley,[3] and Henry.[5] However, as is related to the purpose of this thesis the focus will be on the organometallic chemistry required for a clear understanding of the catalytic processes.

Organotransition metal compounds can best be divided into two categories, those of a metal-carbon, (M-C), σ-bonded nature, where the electron density in the M-C bond is concentrated along the M-C axis, and those where a π-bond is present.

Palladium-carbon σ-bond complexes. The ligands of the M-C σ-bonded complexes are classified into two categories, alkyls such as methyls and hydrides, and aryls such as phenyls and acyls. These ligands are considered as being anionic for the sake of formality. The second category is classified as neutral ligands, examples being carbonyls and isonitriles.

The σ-bonded organopalladium derivatives are generally not stable unless certain stabilizing ligands are present in the complexes. Of these, triphenylphosphine is the most commonly used for catalytic reactions. There are four general methods available for the preparation of palladium(II) σ-bonded organometallic complexes: (1) metathesis reactions of main group organometallics with palladium salts such as halides or acetates;[52,53,54] (equation I.7), (2) oxidative addition of organic halides to palladium(0) complexes, as can be seen in equation I.8. The former method is useful



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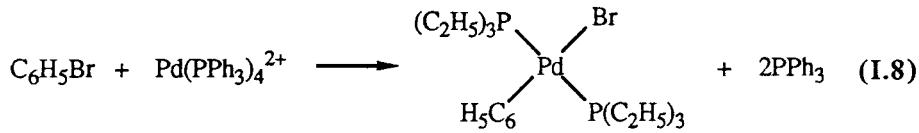
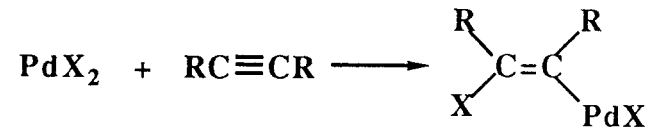


(I.8)

for the preparation of mono and dialkyl or arylpalladium(II) complexes. The latter is only good for preparing monoalkyl-, vinyl-, heterocyclic or arylpalladium compounds; (3) direct metallation of a hydrocarbon, usually an arene or heterocyclic compound with a palladium(II) salt (equation I.9),[55] and (4) addition of a palladium(II) salt to

$$\mathbf{RH + PdX_2 \longrightarrow RPdX + HX} \qquad \text{(I.9)}$$

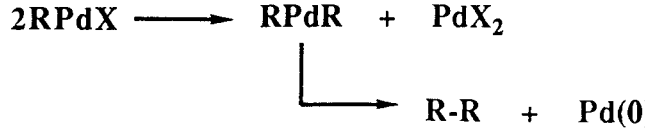
of a palladium(II) salt to an alkene, diene or acetylene, equation I.10.[56]



(I.10)

σ-Alkyl and arylpalladium(II) complexes are intermediates in many palladium-catalyzed reactions. Most of these reactions involve palladium assisted coupling of aryl, alkenyl, allyl, and alkyl derivatives, and carbonylation and decarbonylation reactions of these substrates.[57]

The σ-bonded organopalladium complex can form coupling products via one of three possible routes:[58] (1) disproportionation followed by the reductive elimination of the coupled product as in equation I.11; (2) alkylation or arylation by another

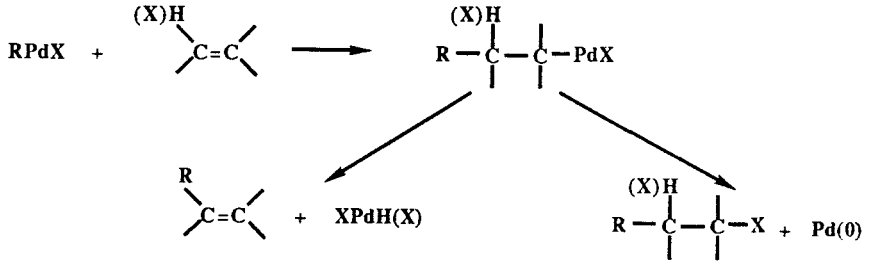


(I.11)

organometallic reagent, or inorganic reagent, to form diorganopalladium compounds which reductively eliminate coupled products, shown in equation I.12; (3) addition

$$\mathrm{RPdX} + \mathrm{R'M} \longrightarrow \mathrm{RPdR'} + \mathrm{MX} \qquad \mathrm{RPdR'} \longrightarrow \mathrm{R\text{-}R'} + \mathrm{Pd(0)} \tag{I.12}$$

or insertion to an alkene, diene or acetylene, followed by palladium hydride or halide elimination forming an alkene, or reductive elimination giving coupled products, see equation I.13.



(I.13)

Palladium hydrides. Hydrides are important in palladium(II) catalytic chemistry since they serve as models for unstable hydride intermediates which are believed to be involved in many catalytic reactions of palladium. Only a few stable palladium(II) hydrides have been isolated and characterized. This is in contrast to platinum(II) which is less labile, and forms stable hydrides. The first palladium(II) hydride was prepared by Brooks and Glocking[65] by the reaction described in equation I.14. The

$$\textit{trans}\text{-}(\mathrm{Et_3P})_2\mathrm{PdCl_2} + \mathrm{CH_3GeH} \xrightarrow{40^\circ\mathrm{C}} \textit{trans}\text{-}(\mathrm{Et_3P})_2\mathrm{P(H)Cl} + \mathrm{HCl} + (\mathrm{CH_3})_3\mathrm{GeCl} + (\mathrm{CH_3})_6\mathrm{Ge_6} \tag{I.14}$$

hydride is stable up to 55°C and has a trans structure both in solution and the solid state. It has also been found that hydrides can be prepared by the addition of HCl to $(Ph_3P)_3PdCO$ and $(Ph_3P)_4Pd$,[66] and by the reduction of *trans*-$(R_3P)_2PdX_2$ with *trans*-$(R_3P)_2NiH(BH_4)$.[67] A dihydride of palladium(II) has been also reported in the

literature.[68]

An important reaction in which a palladium(II) hydride intermediates have been postulated is the Wacker reaction. This is discussed in the section under the Wacker reaction.

Palladium-carbon π-bond complexes. Palladium(II)-π-bonded compounds are classified as non-classical compounds since their bonding is different from that of the classical Werner type complexes or coordination compounds. The π-olefin and acetylene complexes are important intermediates in homogeneous catalysis. Palladium-carbon π-complexes are also used extensively in various catalytic processes due to their high reactivity compared to those of platinum and nickel. Free olefins normally undergo electrophilic attack. However, when bonded to transition metals such as palladium(II), they become susceptible to nucleophilic attack.

The bonding picture for ethylene is similar to that for other olefin complexes, in which platinum is the metal center. The plane of the olefin is perpendicular to the plane of the metal species and the other three ligands. As shown in Figure I.3

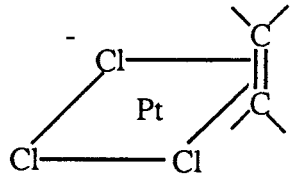


Figure I.3

the overall geometry of Zeise's salt, $K[C_2H_4PtCl_3^-]$, is square planar, as determined by X-ray crystallography. With palladium the picture is similar except that the complex appears to be dimeric in low dielectric constant solvents.[60]

In olefin and acetylene complexes the ligand acts as a two electron σ-donor, the two electrons being the π-electrons of the double bond. These olefin π-complexes are common intermediates in palladium(II)-catalyzed reactions, and are usually very

reactive.[61]

The three carbon allyl radical, CH_2=CHCH·, is also an important π-ligand in palladium(II) catalysis. These are known as π-allylic palladium(II) complexes. The bonding involves all three carbons. It is not seen as a σ and a π bond as in Figure I.4, since the CH_2's are equivalent, but is rather considered from a molecular orbital

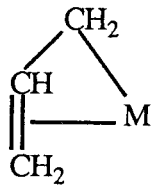


Figure I.4

theory approach, as a molecular orbital involving p orbitals from all three carbons overlapping, all with suitable orbitals of the metal as shown in Figure I.5.

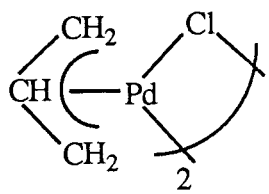


Figure I.5

The allyl group can be treated as a three electron donor, but if the palladium is treated as a +2 oxidation state then it is considered to be a four electron donor. The π-allylic group usually takes up two coordination sites on the palladium(II) to give a halide bridged complex. The plane of the three carbons are at 108°[62] to the plane of the palladium chloride bridge. The five hydrogen atoms are coplanar to the three carbons.

Cyclic π-bonded ligands are also encountered in palladium catalysis. Of these

the most stable are the four electron donor cyclobutadiene group which also takes up two coordination sites,[63] and the cyclopentadienyl ligand, C_5H_5. The cyclopentadiene ligand is quite rare and sometimes forms monocyclopentadienyl complexes.[64]

The two basic reactions in palladium(II) catalysis. It is postulated that most catalytic cycles of transition metals involve one or both of two basic reactions of catalysis: (1) oxidation-addition or its reverse, reduction-elimination; (2) the insertion reaction or its reverse. In this section the two reactions will be discussed with special emphasis on those related to the purpose of this thesis.

(1) The oxidative addition reaction.[69,70,71,72,73] This reaction involves oxidation of the metal and at the same time the coordination number is increased. Generally both the oxidation and coordination numbers are increased by two, as shown in equation I.15. At the same time the coordination number is being increased

$$L_nM^n + XY \longrightarrow L_nM^{n+2}(X)(Y) \qquad (I.15)$$

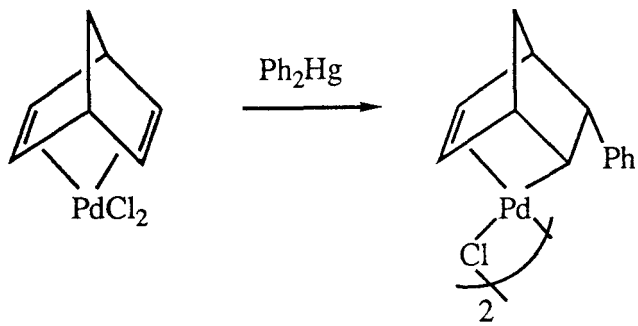
bonds are formed to X and Y. The addendum XY can be both symmetrical and unsymmetrical molecules such as H_2, SO_2, C_2H_4, CH_3I, Cl_2, and O_2. This reaction occurs mainly with d^8 and d^{10} systems. Examples of d^8 systems are Rh(I), Pd(II), and Pt(II), while d^{10} systems include Ni(0), Pd(0), and Pt(0). There are numerous cases of oxidative addition and the reverse reaction being utilized in palladium catalysis.[74]

(2) The insertion reaction. This reaction can be defined as the insertion of an unsaturated molecule between two atoms of another molecule which are originally bonded together, see equation I.16. The addition of palladium(II)-carbon bonds across

$$L_nM\text{-}A + XY \longrightarrow L_nM\text{-}XY\text{-}A \qquad (I.16)$$

double bonds is an important step in a number of catalytic reactions of palladium(II). There are several examples of this type of reaction to give stable adducts.[76,77,78,79] A system in which the insertion reaction and its reverse is widely used is the Heck reaction,[75] shown in equation I.17. Another example with chelating olefins is given

$$\begin{aligned} &ArHgX + PdX_2 \rightleftharpoons [ArPdX] + HgX_2 \\ &[ArPdX] + CH_2{=}CHCH_2X \rightleftharpoons ArCH_2\overset{\displaystyle PdX}{\overset{|}{C}}HCH_2X \\ &\qquad\qquad\qquad\qquad\qquad\qquad \downarrow \\ &\qquad\qquad\qquad\qquad\qquad\qquad ArCH_2CH{=}CH_2 + PdX_2 \end{aligned} \qquad \text{(I.17)}$$



(I.18)

in equation I.18.[80] There are reports of many other such insertion reactions. For an extensive discussion see reference 81.

A very interesting oxypalladation reaction in regard to the Wacker reaction discussed in the next section, is the hydroxypalladation reaction.[82] This will be the focus of the research being described in this thesis.

C. The Wacker Reaction

The Wacker process for the manufacture of acetaldehyde from ethene is the most investigated of all palladium(II) homogeneous catalytic systems. It consists of three separate reactions. The basic reaction, the oxidation of olefins by palladium(II) salts in aqueous solution (equation I.19), was discovered by Phillips in 1894.[83] It

was not until Smidt and co-workers[84] found that $CuCl_2$ could reoxidize the palladium(0) to palladium(II) *in situ* that the reaction became commercially important, (equation I.20). Since cuprous chloride reacts rapidly with O_2 in aqueous acid solution (equation I.21), the net reaction is an air oxidation (equation I.22).

$$PdCl_4^{2-} + C_2H_4 + H_2O \longrightarrow CH_3CHO + Pd(0) + 2HCl + 2Cl^- \quad (I.19)$$

$$2Cl^- + Pd(0) + 2CuCl_2 \longrightarrow PdCl_4^{2-} + 2CuCl \quad (I.20)$$

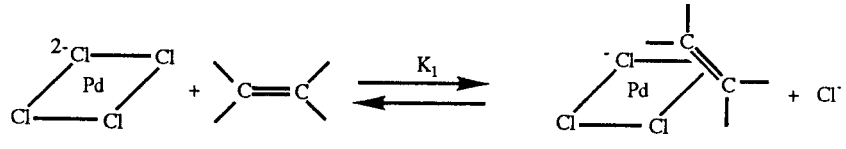
$$2CuCl + \tfrac{1}{2}O_2 + 2HCl \longrightarrow 2CuCl_2 + H_2O \quad (I.21)$$

$$C_2H_4 + \tfrac{1}{2}O_2 \longrightarrow CH_3CHO \quad (I.22)$$

Because of its basic importance to the field of transition metal catalysis, the reaction has been studied by a number of groups, and there are several controversies in regard to the interpretation of the data.[85a] The rate expression is given by equation I.23. It is agreed that the first step in the reaction sequence is the

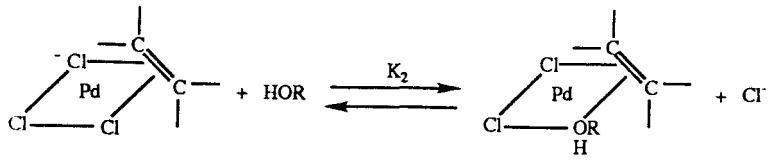
$$\text{Rate} = \frac{k[PdCl_4^{2-}][\text{olefin}]}{[H^+][Cl^-]^2} \quad (I.23)$$

equilibrium resulting in a π-complex formation as given in equation I.24. This



(I.24)

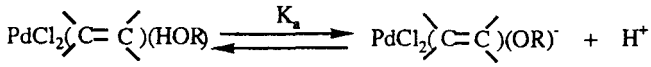
accounts for the first chloride inhibition term in the rate expression. The second chloride inhibition term arises from the displacement of a second chloride by the solvent, water or methanol, in an equilibrium step, shown in equation I.25. The third step, related to the acid inhibition term, has generated controversy. The rate



(I.25)

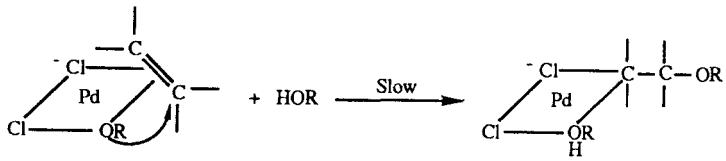
expression is consistent with the following routes.

(1) There is another equilibrium to release a proton as shown in equation I.26,



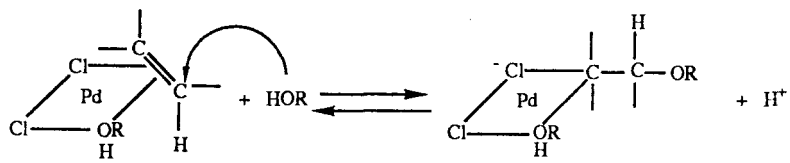
(I.26)

followed by the *cis* addition of coordinated hydroxide or methoxide, (oxypalladation; or more specifically hydroxypalladation if R = H), in the slow step, equation I.27.



(I.27)

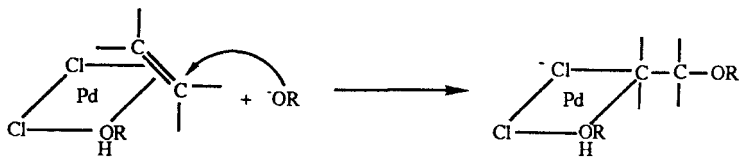
(2) A second mechanism involves *trans*- attack by external solvent in an equilibrium step, equation I.28. This equilibrium would not be detected unless some



(I.28)

change in the olefin such as isomerization occurred every time the addition-elimination sequence took place. For most olefins no such change is possible even if the sequence is stereospecific.

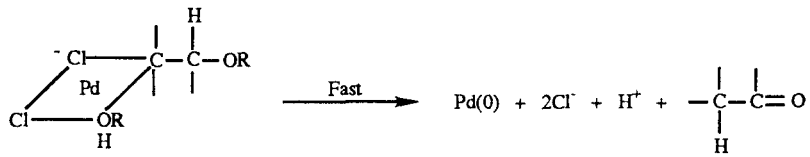
(3) Another possible mechanism is the external attack by ^{-}OR, as shown in equation I.29, In two aqueous cases, it has been shown to be impossible because



(I.29)

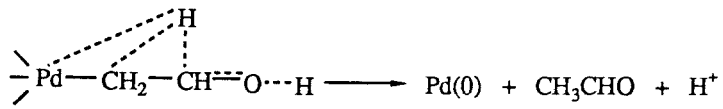
the attack would have to be faster than a diffusion controlled process in aqueous solution.[86] The calculated k for this attack was of the order of 10^{13} $M^{-1}s^{-1}$, while that of a diffusion controlled process is of the order of 10^{9} $M^{-1}s^{-1}$.[27] It is clear that the rate would have to be 10,000 times faster than a diffusion controlled reaction for this mechanism to be possible. It is also argued that the ^{-}OR will not attack the negatively charged trichloropalladium(II)-π-complex because of electrostatic considerations but that it could easily attack the neutral species as indicated in equation I.29.

The final step in both mechanisms is the oxidative decomposition of the oxypalladation intermediate, involving a hydride shift, as summarized in equation I.30.



(I.30)

Henry postulated in 1964, that this step occurs via an activated complex in which palladium is assisting in a hydride shift as it leaves with its electrons.[86a] Later experimental results from the oxidation of C_2H_4 in CH_3OD, indicated that 1,1-dimethoxyethane containing no deuterium was produced. This led Moiseev and Vargaftik[87a] to propose that the decomposition step in the aqueous oxidation occurred via a similar route to that previously proposed by Henry, where palladium(II) assisted the hydride shift from one carbon to the other without the



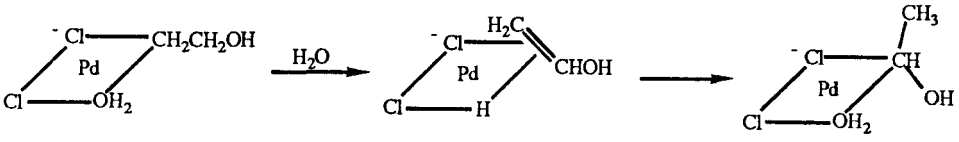
(I.31)

distinct state of formation of a palladium(II) hydride, equation I.31. This was supported by the thought that there was a fast electronic rearrangement to convert the alcohol to a carbonyl group. This theory was contradicted by Henry and Lee[42]

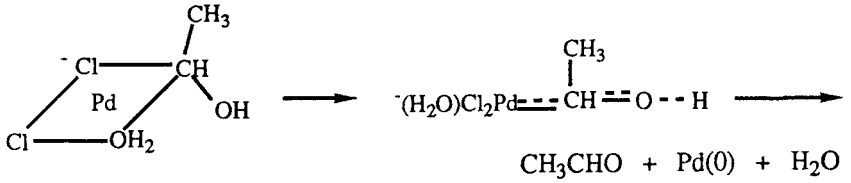
who showed that this mechanism should give vinyl ethers as the initial product in methanol, which upon hydride elimination would result in the addition of methanol across the double bond, and if carried out in CH_3OD should contain one deuterium, equation I.32. This showed that the actual experimental results were inconsistent

$$CH_2{=}CHOCH_3 + CH_3OD \longrightarrow CH_2DCH(OCH_3)_2 \qquad (I.32)$$

with the mechanism proposed by Moiseev. A later proposal for the aqueous system was that this intermediate involves a palladium(II)-hydride vinyl alcohol complex.[88] This mechanism for ethylene in water is briefly summarized in equations I.33 and I,34. This decomposition scheme would be analogous in methanol and explains why

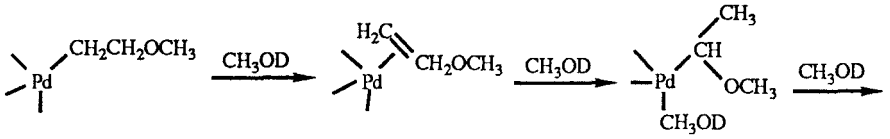


(I.33)



$$CH_3CHO + Pd(0) + H_2O + 2Cl^- \qquad (I.34)$$

there is no deuterium incorporated in the product when the solvent is CH_3OD (equation I.35).



(I.35)

$$CH_3CH(OCH_3)_2 + Pd(0) + H^+$$

A later proposal by Jira is shown in equation I.36.[88a] This mechanism involves the complete elimination of palladium(II)-hydride followed by readdition putting the palladium(II) on the carbon containing the hydroxyl group. This intermediate then

decomposes to give the observed oxidation products. There were many arguments given against this mechanism until stable vinyl alcohol π-complexes of iron were

$$^{-}Cl(OH)Pd(C_2H_4) \underset{}{\overset{H_2O}{\rightleftharpoons}} {}^{-}Cl_2(H_2O)PdCH_2CH_2OH$$

$$^{-}Cl_2(H_2O)PdCH_2CH_2OH \overset{-H_2O}{\rightleftharpoons} {}^{-}Cl_2(H)Pd(CH_2{=}CHOH)$$

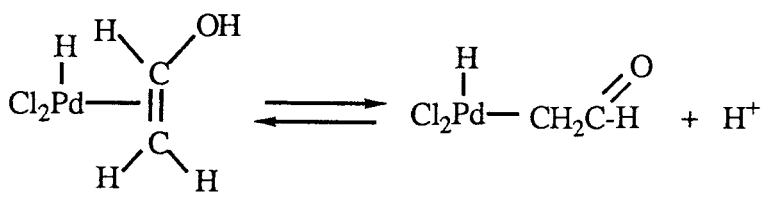
I.a

$$\textbf{I.a} \overset{+H_2O}{\rightleftharpoons} {}^{-}Cl_2(H_2O)PdCH(OH)CH_3 \quad \textbf{I.b} \qquad \text{(I.36)}$$

$$\textbf{I.b} \xrightarrow[H_2O]{\text{Slow}} CH_3CH(OH)_2 + PdCl_2^{2-} + H^+$$

$$CH_3CHO + H_2O$$

prepared,[87b,87c] thus showing that kinetically stable palladium(II) complexes such as **I.a**, are reasonable. However their proposal that the slow step of the reaction is the decomposition step was not consistent with the isotope effect studies of deuterated



I.a **I.c** (I.37)

$$\textbf{I.c} \longrightarrow CH_3CHO + Pd(0) + Cl^-$$

studies of deuterated ethylene. A reasonable variation of the scheme of Jira and coworkers was outlined by Henry,[136] and is shown below in equation I.37.

D. The Problem

The controversy surrounding the mode of hydroxypalladation in the Wacker reaction deserves some attention. As mentioned in the previous section this controversy concerns a proposed *cis* mode of hydroxypalladation from a coordinated OH group, as opposed to a *trans* mechanism proposing the external attack of a water molecule on the palladium-π-complex.

The experimental arguments in favor of the *cis* addition mechanism are:

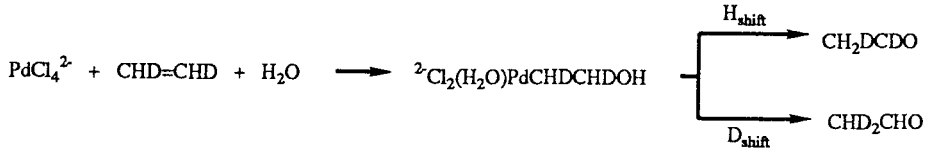
(1) Comparisons of the kinetic and competitive isotope effects. This was carried out by Henry.[86a,89] The kinetic isotope effect on this system using ethene-d_4 was studied. When C_2H_4 was oxidized in D_2O, the product acetaldehyde[96] was undeuterated. The decomposition therefore must incorporate the transfer of a proton from one carbon to the other. Also when C_2D_4 was oxidized in H_2O, C_2D_4O was formed, equation I.38, indicating that a deuteride shift occured in the decomposition

$$C_2D_2 + PdCl_4^{2-} \xrightarrow{H_2O} CD_3CDO + Pd(0) + 2HCl + 2Cl^- \quad \text{(I.38)}$$

step. This transfer of proton would be expected to involve a positive isotope effect if deuterated ethylene was oxidized in water, and specifically a kinetic isotope effect would be expected if the deuterium shift occurred in the rate determining step. The value of the isotope shift, k_H/k_D was 1.07, indicating that the rate of C_2D_4 oxidation was the same as that of C_2H_4 within experimental error.[86a] This suggests that the hydride-shift step occurs after the rate determining step as shown in equations I.26 and I.27. There is some uncertainty with this as isotope effects in the

decomposition of such adducts have not been studied.

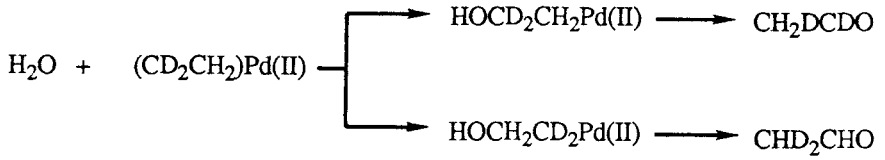
A competitive isotope effect was also looked at using *cis*- and *trans*-CHD=CHD as substrate. As can be seen from equation I.39 either mode of hydroxypalladation



(I.39)

will give a choice of H or D transfer. The ratio of the tendencies for H to transfer as opposed to D is a measure of the isotope effect. The ratio of deuterated isomers, CH_2DCDO/CHD_2CHO, was between 1.8 and 2.0. Another study using mass and microwave spectroscopies, indicated a k_H/k_D of 1.8 - 2.0. These results of the isotope effects are in support of the conclusion that hydroxypalladation is the rate determining step.[86a,95,97]

(2) Secondary isotope effects. These effects are inconsistent with equilibrium oxypalladation, equation I.28.[88b,90] Saito and co-workers[90] oxidized ethene-1,1-d_2 in water under Wacker conditions and their results suggested that the process of 2-hydroxyethylpalladium(II)-σ-complex formation is rate determining.[98] They found that the complexes, $HOCD_2CH_2PdCl_2^-$ and $HOCH_2CD_2PdCl_2^-$, formed from $CH_2=CD_2$, were converted rapidly into CH_2DCDO and CHD_2CHO, (equation I.40). The ratio of



(I.40)

CH_2DCDO/CHD_2CHO was 0.89. This reflected a secondary deuterium isotope effect for the hydroxypalladation step of the Wacker reaction. The secondary deuterium isotope effects for the addition to olefins are generally less than 1.0, suggesting an sp^3 character for the carbon in the transition state. The ratio of the secondary deuterium effects indicates that the sp^3 character is larger for the α carbon than the

β carbon, and shows that the transition state for 2-hydroxyethylpalladium(II) σ-complex formation is preferentially of a σ-bonding nature with the palladium(II) rather than the completely symmetrical π-coordinate structure. This strongly supports the rapid formation of the C=O group via a hydride shift, assisted by palladium(II)[86a] in a syn manner, following the rate determining step. The results suggested *cis* attack of the hydroxide to olefin as the rate determining step.

(3) Studies on the oxidation and isomerization of deuterated allylic alcohol.[5,106] In order to detect oxypalladation, an allyl alcohol which could easily show a change such as isomerization, every time oxypalladation occurs was utilized. The oxygen-18 exchange and deuterium label isomerization scheme shown in equation I.41 was

$$CH_2{=}CHCD_2{}^{16}OH + Pd(II) + H_2{}^{18}O \rightleftharpoons H^{18}OCH_2\underset{}{\overset{Pd(II)}{C}}HCD_2{}^{16}OH + H^+$$

$$\rightleftharpoons H^{18}OCH_2CH{=}CD_2 + Pd(II) + H_2{}^{16}O \qquad \textbf{(I.41)}$$

studied. At high chloride and acid concentrations where oxidation is very slow, a non-oxidative oxypalladation was observed to proceed. This has a different rate expression given in equation I.42. This oxypalladation has single chloride inhibition

$$\textbf{Rate} = \frac{k[PdCl_4{}^{2-}][\text{allyl alcohol}]}{[Cl^-]} \qquad \textbf{(I.42)}$$

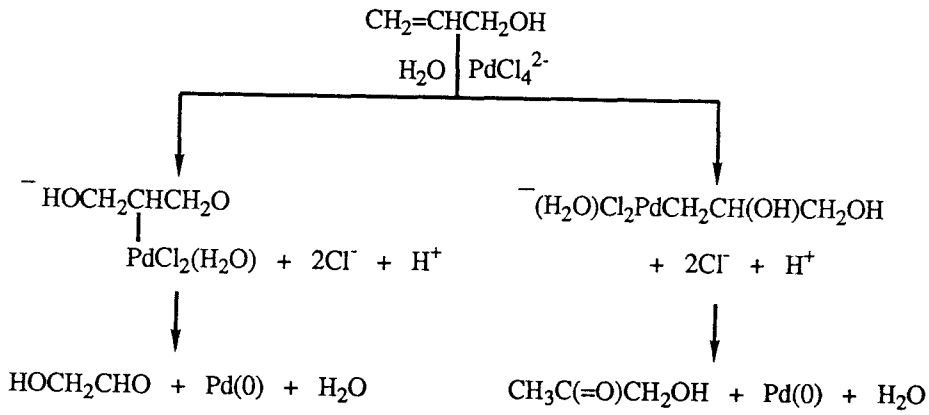
term and no acid inhibition term, indicating that high chloride inhibits oxidation more than this mode of non-oxidative oxypalladation. The kinetics for this substrate and the product distribution were also reported under Wacker oxidation conditions,[91] $[Cl^-]$, $[H^+] < 1.0$ M. The rate expression was identical to the Wacker rate expression, (equation I.23). The product distribution is shown in equation I.43.

3-Hydroxypropanal and 1-hydroxy-2-propanone were as predicted on the basis of

$$CH_2{=}CHCH_2OH + H_2O \xrightarrow[-H^+]{PdCl_4^{2-}} \begin{matrix} CH_2{=}CHCHO & 30\ \% \\ CH_3COCH_2OH & 15\ \% \\ HOCH_2CH_2CHO & 40\ \% \end{matrix} \qquad (I.43)$$

Wacker chemistry. This is similar to the oxidation of propene, where the products, propanal and acetone can be explained by Markovnikov and non-Markovnikov addition. The reaction scheme for allyl alcohol is outlined in Scheme I.1. Acrolein

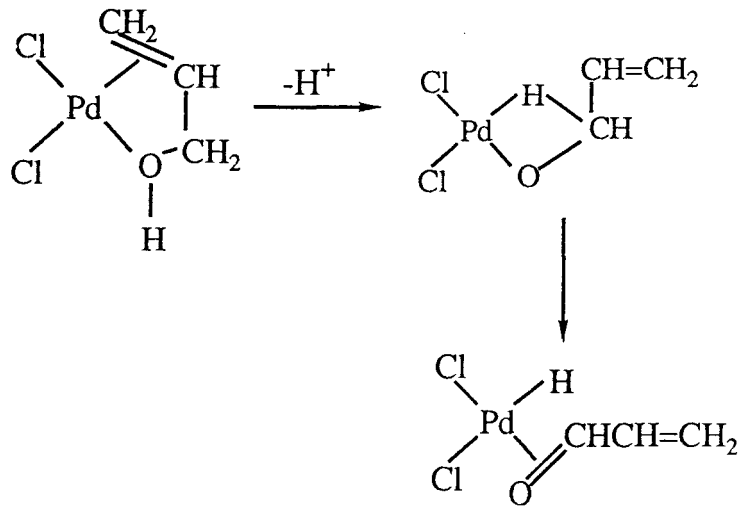
Scheme I.1



was also obtained, and was previously postulated to arise from the dehydration of 3-hydroxypropanal. However it was demonstrated that it was being produced by the direct hydrogen abstraction from the alcohol carbon of the starting allyl alcohol. Similar results of past works, in which saturated alcohols have been oxidized by palladium(II) salts to aldehydes and ketones,[92,93,94] have been published. A mechanism consistent with the product and obeying the rate expression given in equation I.23, has been shown in Scheme I.2.[91] The unreacted alcohol was monitored

for the extent of isomerization under the conditions of rapid oxidation, and less than

Scheme I.2



3 % isomerization was detected. This means that oxypalladation at low chloride and acid conditions is not an equilibrium process for allyl alcohol oxidation and presumably not for ethene oxidation, but rather the slow step of the oxidation.

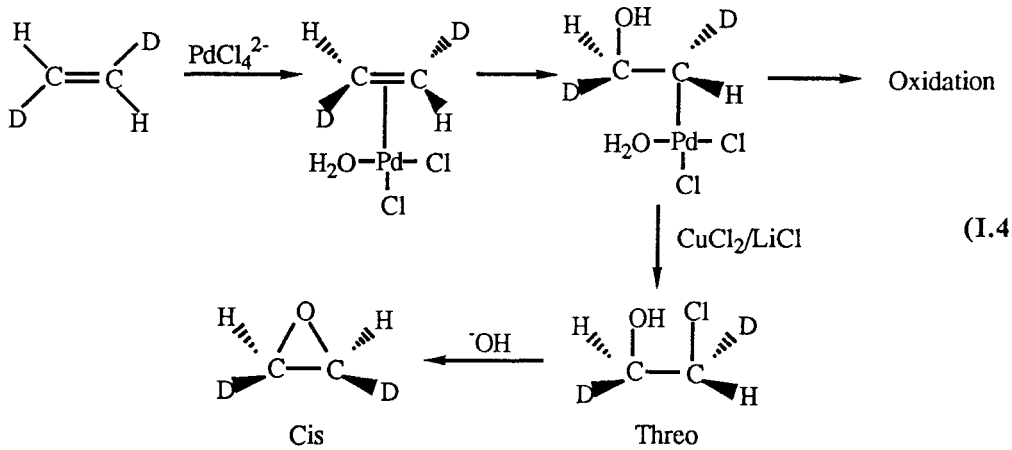
More recently further evidence in support of the *cis*-oxypalladation mechanism, has been reported in the literature. Experimental and theoretical results from the investigation of the methoxypalladation of dichloro(2,2,N,N-tetramethylbut-3-enylamine)palladium(II) have shown the mechanism to proceed via a *cis*-methoxypalladation pathway.[85b] Work done by Bryndza on the reaction of $(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2Pt(CH_3)(OCH_3)$ with tetrafluoroethylene has shown that there is a rate limiting insertion of tetrafluoroethylene into the Pt-O bond.[85c]

The evidence for *trans*-oxypalladation, equation I.25, arises from stereochemical studies.[100-103] Since aldehydes and ketones formed under Wacker conditions, [Pd(II)] = 0.005 - 0.04 M; $[Cl^-]$ = 0.1 - 1.0 M; $[H^+]$ = 0.04 - 1.0 M in 100 % aqueous solution, do not give stereochemical information, the reaction conditions must be changed to

give other products that do give an indication of whether they were formed by *cis*- or *trans*-addition. For example Stangl and Jira[104] in 1970 found that at high concentrations of $CuCl_2$ in the presence of high chloride concentrations the product became 2-chloroethanol, equation I.44. The $CuCl_2$ apparently interacts with the

$$C_2H_4 + CuCl_2 + H_2O \xrightarrow{PdCl_4^{2-}} ClCH_2CH_2OH + CuCl \qquad (I.44)$$

oxypalladation adduct causing it to decompose differently than in the absence of $CuCl_2$. Bäckvall and co-workers,[101] using cis and trans-ethene-1,2-d_2, were able to show that the products under these conditions of high chloride and $CuCl_2$ were consistent with *trans*-oxypalladation. As shown in equation I.45 trans-1,2-



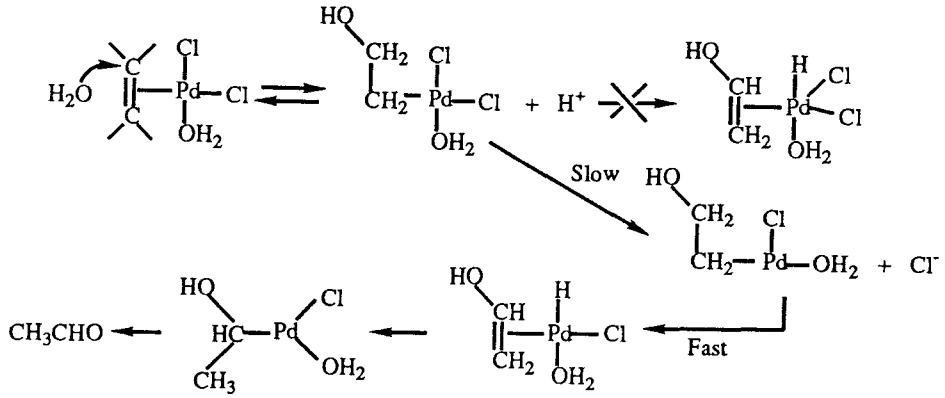
(I.45)

dideuteroethene produced threo-2-chloroethanol at $[Cl^-]$ = 3.0 M and high $CuCl_2$ concentrations. Cis-1,2-dideuteroethene gave erythro-2-chloroethanol. In order to explain the isotope effects, which require the hydride shift to occur after the rate determining step, and in order to avoid invoking a third chloride inhibition, these workers proposed that the loss of a third chloride from the oxypalladation intermediate as the slow step of the reaction, Scheme I.3.

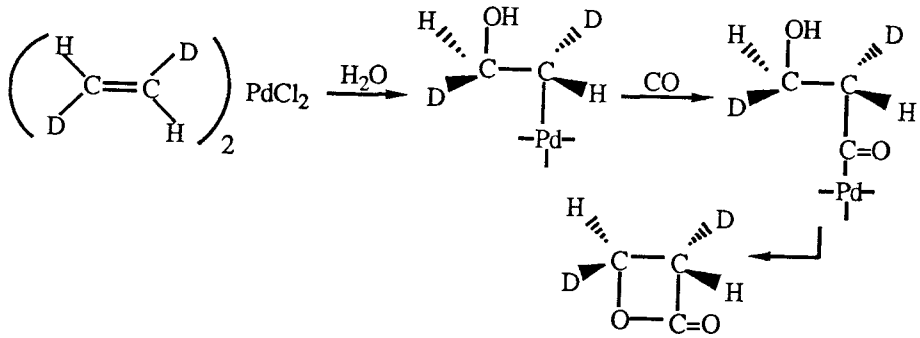
Another type of stereochemical study, involving the capture of the intermediate σ-bonded species by inserting CO in the palladium(II)-carbon bond, thus generating a

product whose stereochemistry can be determined, has been carried out in 2 % water in acetonitrile using 1,2-dideuteroethene.[115] Equation I.46 gives the reaction

Scheme I.3



sequence. The trans-2,3-dideutero-β-propriolactone product is consistent with trans



(I.46)

hydroxypalladation.

This last result does not give a true indication of the actual stereochemistry of the hydroxypalladation step under the conditions in which the kinetics of the palladium(II) oxidation of ethylene was determined. There are important differences between the conditions used in this study and those under which the kinetics were determined:

1. The solvent was not pure water.
2. The temperature used was -20 to -25 °C rather than 25 °C.
3. There was no excess chloride present, and so the palladium(II)-π-complex could not be formed.
4. The bis-ethylene complex was used. This could be attacked trans for the same reasons as the cyclic olefins discussed later.

Theoretical work has been published more recently in support of the *trans*-mechanism, and has shown that by using an effective core potential *cis*- migration is possible only for anions such as H^- and CH_3^-, but not for OH^- and F^- anions.[101b]

There are two experimental results and data that has cast some doubt on Bäckvall's mechanism as summarized in Scheme I.3. The data shown in Table I.2 are

Table I.2

Ethylene Chlorohydrin Production

$$2CuCl_2 + C_2H_4 + H_2O \xrightarrow{PdCl_4^{2-}} 2CuCl + ClCH_2CH_2OH + HCl$$

$[PdCl_4^{2-}]^a$	$[CuCl_2]^a$	$[Cl^-]^a$	CH_3CHO^b	$ClCH_2CH_2OH^b$
0.0164	4.0	0.0	1.26	0.05
0.0164	4.0	10.0	0.36	1.60

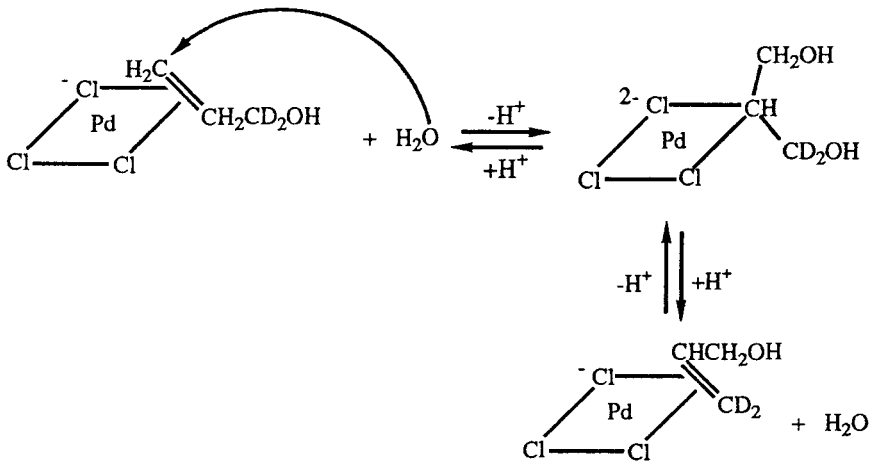
[a]units are in moles L^{-1}. [b]Yields are in grams.

those of Stangl and Jira in their original studies.[105] This showed that not only high $CuCl_2$ concentrations but also high chloride concentrations are required if the ratio of chloroethanol to acetaldehyde is to be high, $[CuCl_2]$ = 2.5 - 4.0 M; $[Cl^-]$ = 3.0-10.0 M. This is not the result expected if both products proceed through a common intermediate, but is expected if chloride is inhibiting acetaldehyde formation, a

reaction inhibited more strongly than chloroethanol formation by chloride. This suggested that a second mode of oxypalladation leading to chloroethanol in the presence of high concentrations of $CuCl_2$ could have been operative.

Studies of the oxidation and isomerization of deuterated allyl alcohol[86b] has given support to the suggestion that a second mode of oxypalladation is active at high concentrations of chloride ions. The rate expression for exchange is consistent with the reaction scheme shown in Scheme I.4. The single chloride inhibition term

Scheme I.4



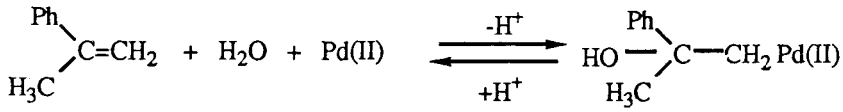
results from replacement of a chloride by olefin in the coordination sphere of palladium(II). Since there is no second chloride inhibition, this means that water must attack from outside the coordination sphere of the metal as shown, which is consistent with the stereochemistry of chloroethanol formation. The tacit assumption in these studies is that the mode of oxypalladation is independent of the reaction conditions and substrate structure. Consider the hydroxypalladation of cyclohexadiene to give π-allyl palladium(II) complex under non-Wacker conditions, 8 % water in acetone, the structure of which is consistent only with trans addition.[100]

This is not surprising since even in aqueous solution under Wacker conditions the cyclic olefins,[88b,107] and 2-cyclohexenol,[108] are oxidized according to the rate expression given by equation I.40. If these analyses are right, the stereochemistry at higher chloride is not related to the mode of hydroxypalladation at lower chloride concentrations under Wacker conditions.

E. Scope of Study

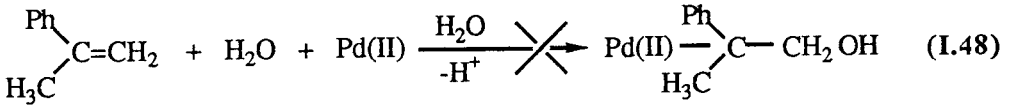
The aim of this study is the development of mechanistic tools, and their use in obtaining unambiguous information on individual steps in palladium(II) catalysis and the effect of reaction conditions, ligands and substrates on these steps. The two mechanistic probes that will lead to new advances in this area are: (1) a kinetic probe which will allow the determination of the rate expression for a single step such as oxypalladation. (2) a stereochemical study which will delineate the mode of attachment of palladium(II) and $^{-}$OR to the olefin under the conditions which the kinetics are studied. The substrate used for the stereochemical studies should obey the oxidation kinetics, and thus a stereochemical probe used for Wacker chemistry should be oxidized according to the expression given by equation I.23.

Kinetic Probe. Let us consider the reason why olefins, disubstituted on one vinylic carbon, are not oxidized to the usual products, but rather tend to be eventually oxidized by π-allylic routes,[109] or undergo oxidative coupling.[110] One example of such an olefin is α-methyl styrene, $Ph(CH_3)C{=}CH_2$. The Wacker-type oxidation products are formed by oxypalladation followed by β-hydride shift giving aldehydes and ketones in water and acetals and ketals in alcohol. The addition shown in equation I.47, although it would be expected to occur because of the small



(I.47)

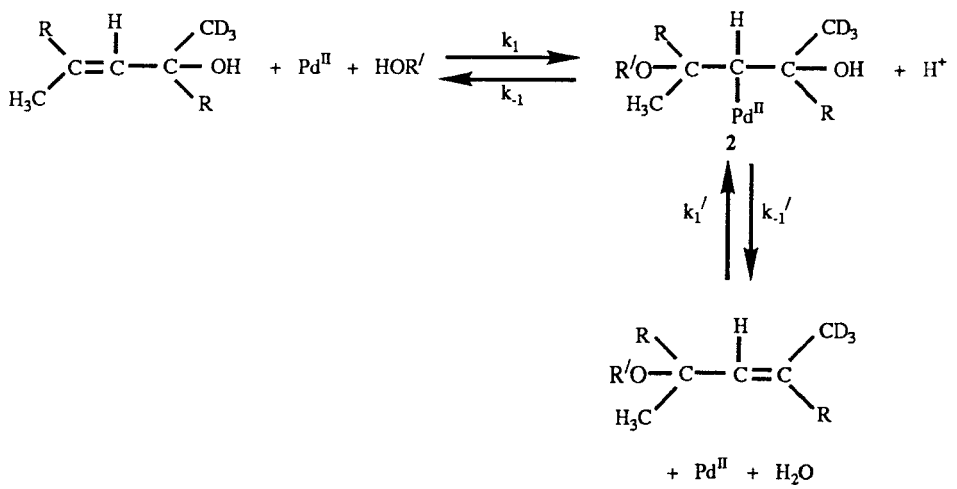
size of the hydroxyl group, cannot lead to oxidation products, since there are no β-hydrogens to shift. Alternatively the mode of addition shown in equation I.48 does



(I.48)

not occur because of steric hindrance between the large Pd(II) moiety and the substituents. If some measurable change can be made to occur every time oxypalladation shown in equation I.47 takes place, then a means of measuring mechanisms independent of oxidation is available. With this introduction specific examples where such information can be obtained in methanol and in water will be considered. The isomerization and exchange sequence shown in Scheme I.5 will be

Scheme I.5



studied in water and in methanol. In methanol R- will be methyl groups, and in water they will be trifluoromethyls.

How can this probe give information on the rate expression for oxypalladation? The intermediate 2 has a OR′ and a OR group on its β-position but no β-hydrogens to shift for oxidation to a carbonyl product. Therefore it can only eliminate one of

the OR′ groups to give allylic alcohol in water, or allylic alcohol or ether in methanol. In water the two hydroxyl groups are in chemically similar environments. Thus except for a very small deuterium isotope effect, the probability of elimination is equal. This means that $k_{-1} = k'_{-1}$ and the hydroxypalladation step is rate determining, for both exchange and isomerization. In other words hydroxypalladation must be rate determining for a symmetrical exchange with a symmetrical allylic alcohol because exchange must occur half the time that hydroxypalladation occurs.

Let us assume that the exchange in Scheme I.5 is being studied under Wacker conditions and there is external attack of HOR′. The pre-equilibriums shown in equations I.24 and I.25 will occur first to give a squared chloride inhibition. If external, *trans*-oxypalladation is the correct mechanism, then the external attack of water or methanol would be the next step. Since the proton loss would be occurring after the slow step of the reaction the proton inhibition term will not appear in the rate expression. The rate expression for scheme I.5 will be given by equation I.49,

$$\text{Rate} = \frac{k[PdCl_4^{2-}][\text{allyl alcohol}]}{[Cl^-]^2} \qquad \text{(I.49)}$$

and the mechanism will be the reaction sequence in equation I.28. If the mechanism is given by equations I.26 and I.27, the rate expression will be given by equation I.23, since the proton loss will have occurred before the rate determining step.

In methanol the system as described by scheme I.2 will also be studied, with R- being CH_3- and -OR′ as $-OCH_3$. The results will be interpreted similarly to those of the studies in water. However this system in methanol will also be aimed at clarifying the mechanism of exchange of allylic and vinylic alcohols and ethers to give new vinylic and allylic ethers, which is presently poorly understood.[105] Let us again consider the exchange and isomerization reaction shown in scheme I.5.

Palladium(II) will add to the center carbon of 1, to give the intermediate 2. Having no β-hydrogens to shift to give oxidative decomposition, only exchange and isomerization can occur. This mechanistic probe will be used to determine the types of oxypalladations which occur under various reaction conditions. Allyl alcohols containing β-hydrogens will be reacted to see which of these oxypalladation routes are oxidative and which will give only exchange.

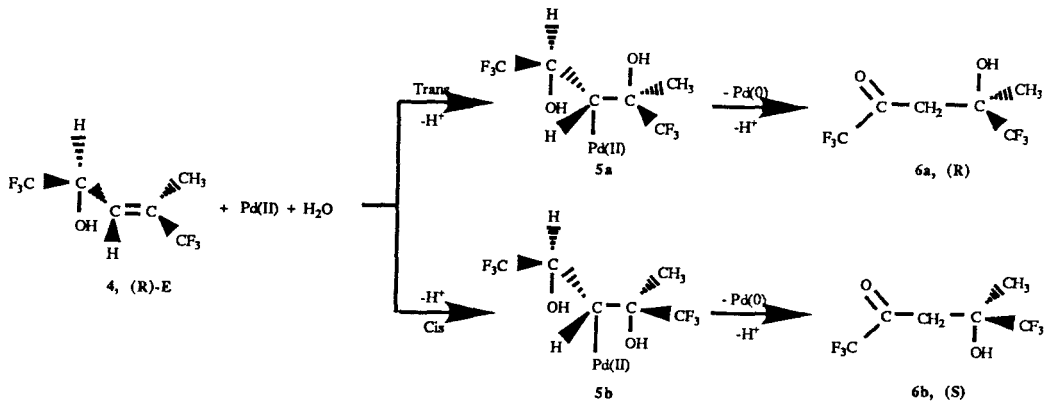
These studies are likely to shed light on the controversy of the Wacker chemistry, in both water[86,111] and methanol.[42] The rate expression for acyclic olefin oxidation under Wacker conditions in methanol is given by equation I.20, and so it is apparent that an analogous mechanism is operative in both solvents. In any case a comparison of the rate expressions for exchange and oxidation under conditions where oxidation occurs, and obeys equation I.23, would give considerable insight into the mechanism of the Wacker chemistry. Under conditions where oxidation is very slow, $[Cl^-] > 3.0$ M, a non-oxidative exchange reaction was found in aqueous solution and thus a similar non-oxidative exchange may be expected in methanol. This non-oxidative exchange has the rate expression given in equation I.42.

Stereochemical Probe. Stereochemical studies have been carried out in some catalytic reactions, where the products permit such determination. Examples of such products include vinylic and saturated esters in acetic acid,[112] and the stereospecificity of palladium(II) catalysis has been put to use by Trost[113] and others.[114] In two of the more important solvents, water and methanol, the products, aldehydes and ketones in water and acetals and ketals in alcohol, do not permit straight forward determination of stereochemistry. As previously discussed, stereochemistry was determined in the aqueous system from side products which were assumed to arise from the same intermediate as the carbonyl products. It is however

preferable to determine stereochemistry on the actual Wacker type products. A proper definition for stereochemistry can be accomplished using the technique of chirality transfer, in the oxidation of certain chiral allylic alcohols. Partial 1,2-chirality transfer was previously demonstrated for the palladium(II)-catalyzed addition of a phenyl group, the Heck reaction, to chiral 3-methyl-3-buten-2-ol.[114]

Consider the chiral allylic alcohol **4**, in the reaction sequence shown in Scheme I.6. There is restricted rotation of chiral alcoholic center and it has been shown

Scheme I.6



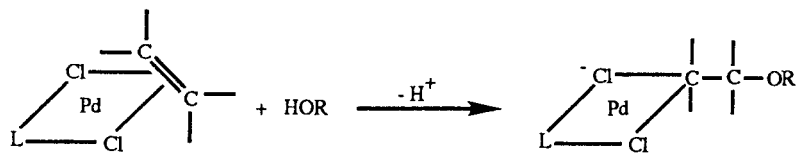
that the OH is restricted to a position below the plane of the molecule.[116] Invoking Cram's rule,[117] it can be expected that the palladium will add to the same side as the OH stereofacially.[118,119] This has been proposed for diversely catalyzed epoxidation reactions[120,121] in which a strong directing effect of hydroxy group[122] predominated over those of bulky substituents. If the starting alcohol is one specific enantiomer of **4**, a stereoselective oxypalladation is predicted to create a chiral center at the carbon bearing the new hydroxyl substituent in the intermediate **5**. This new chiral center is retained upon oxidation, detachment of palladium(0), to give **6**, and a new chiral center is created at the carbon to which the incoming hydroxide

is transferred. If the initial absolute configuration is known, the configuration of the product should indicate the stereochemistry of the hydroxypalladation step. For *trans*-hydroxypalladation a retention of configuration, **6a**, is expected while for *cis*-hydroxypalladation an inversion of configuration is expected, as in **6b**.

Effect of Ligands. The mode of oxypalladation and the stability of the intermediate adduct depends on the ligands around the palladium. An example of a relatively stable intermediate is that shown in equation I.30 and the intermediate in scheme I.4. There is no doubt that the *trans* attack shown in Scheme I.3 occurs as well as in other systems.[123,124] For instance a catalyst for oxidation by hydride shift or elimination,[125] should have rapid rates of oxypalladation and very unstable intermediates. On the other hand catalysts for exchange,[110c] should have stable oxypalladation adducts. Catalysts for carbonylation,[126] will also require stable intermediates and coordination sites for CO. Oxidant promoted reactions[98] will require the catalyst to form a stable adduct and probably a bridging group for electron transfer from the palladium to the oxidant.

Once the mode of oxypalladation by $PdCl_4^{2-}$ has been defined in water and methanol the effect of a number of variables which could help in the design of new catalysts will be studied. A partial list includes: (a) effect on stereochemistry and intermediate stability if one chloride is replaced with a strongly complexing neutral ligand, and (b) effects of substitution at two or more positions with a bidentate or tridentate neutral ligand.

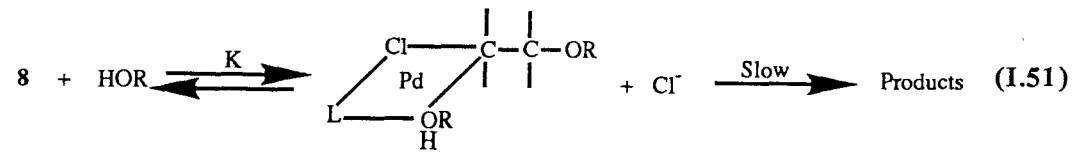
Let us consider the effect, on the oxypalladation step, of placing a strongly complexing neutral ligand, in the coordination sphere of the catalyst. One effect should result in a charge decrease in the initial π-complex, **7**. Thus in equation I.50



7 **8** **(I.50)**

the π-complex, 7, is neutral rather than negatively charged as in equation I.24, and would be much more susceptible to an external attack. The chloride may be expected to be inert to replacement by water since a cationic complex would result. Both these factors would discourage internal attack and so external attack would be predicted to be dominant. This analysis can be tested by exchange and isomerization kinetics, as described in scheme I.5. Again external attack would be expected to give a rate expression similar to equation I.42, with a single chloride inhibition and no acid inhibition term. On the other hand internal attack is expected to give a rate expression similar to equation I.23, with both acid and squared chloride inhibition terms since both the olefin and HOR groups must enter the coordination sphere of the catalyst. If the attacking species is $^-$OR then the rate expression will be as in equation I.23 including both squared chloride and acid inhibition terms, but if it is HOR we should get the rate expression as in equation I.47 with only a squared chloride inhibition.

The stability of the oxypalladation adduct is also an important mechanistic consideration if external attack occurs. In equation I.50 this adduct, **8**, would be expected to have some stability, since hydride shift to initiate oxidation requires a vacant coordination site. There is kinetic evidence that this vacant or weakly coordinated site is required for hydride shift initiated decomposition of oxypalladation intermediates in non aqueous solution,[127] and further evidence that such sites are required for the decomposition of platinum(II) alkyls.[128] Dissociation of a chloride from the oxypalladation intermediate, in equation I.51, would occur more readily than



(I.51)

from the π-complex intermediate, 7, since the oxypalladation intermediate would be

more negatively charged. In this case isomerization is predicted to have a single chloride inhibition term as in equation I.42, while oxidation could resemble either equation I.23, with both squared chloride and acid inhibition terms or equation I.47 with only a squared chloride inhibition term. Also in this case the oxypalladation shown in equation I.50 may be reversible. An olefin which can undergo oxidation but also give an indication of whether it undergoes oxypalladation without oxidation could serve this purpose. If the kinetics of exchange and oxidation follow the postulated trend, this would be strong evidence for the need, in aqueous system, for a labile coordination site on palladium(II) before hydride transfer can occur.

CHAPTER II

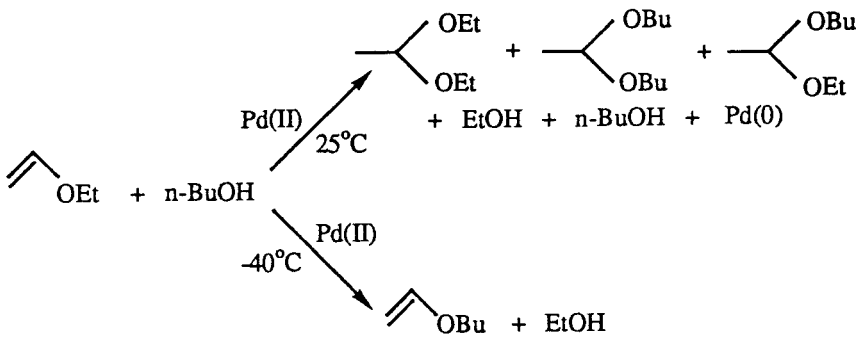
PALLADIUM(II) CHLORIDE CATALYZED EXCHANGE AND ISOMERIZATION OF 2-METHYL-d_3-4-METHYL-3-PENTEN-2-OL AND ITS ETHYL ETHER IN METHANOL.

A. Purpose

The palladium(II) catalyzed exchange of vinylic and allylic esters, chlorides and ethers with alcohol solvents has been the subject of several patents.[129] The most fundamental mechanistic study was by McKeon and coworkers[110a,b] who found that the ether exchange was not as readily carried out as the ester exchange in carboxylic acid solvents.[110c] When the reaction with vinyl ethers is carried out at room temperature, the only products are acetals and alcohols with the precipitation of palladium metal. At -40°C an equilibrium mixture of vinyl ethers is obtained with no precipitation of palladium metal. An example is the reaction of ethyl vinyl ether with *n*-butanol shown in Scheme II.1, the Pd(II) being in the form of $(PhCN)_2PdCl_2$.

Further studies indicated that the oxidation reaction forming acetals, which occurred above -25°C, was catalyzed by HCl formed when $(CH_3CN)_2PdCl_2$ was reduced. If the reaction mixture is buffered using NaH_2PO_4, the exchange to give vinyl ethers occurred at 25°C although some palladium metal still precipitated. Finally two chelating diamine complexes of palladium(II) acetate, (L-L)$Pd(OAc)_2$ (L-L = 2,2'

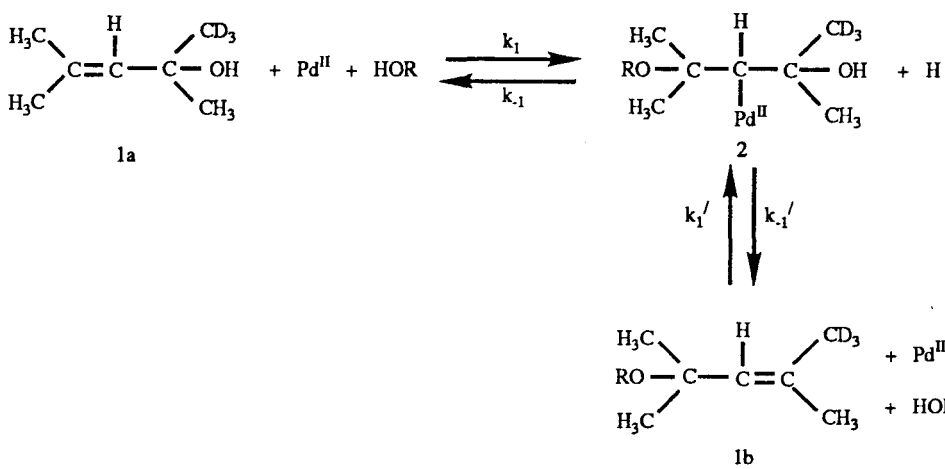
Scheme II.1



-bipyridine or 1,10-phenanthroline) were found to be effective catalysts for exchange at temperatures up to 80°C.

Thus the mechanism of exchange to give vinyl and allylic ethers is poorly understood and needs clarification if conditions for achieving useful exchange reactions are to be defined. The strategy which will be employed involves kinetic studies of the exchange and isomerization of tetrasubstituted allylic alcohols which *cannot* be oxidized by hydride shift to give acetals and ketals. Consider the exchange and isomerization reactions shown in Scheme II.2 where the allyl alcohol, **1a**, is prepared by adding methyl-d_3 magnesium bromide to mesityl oxide, R = H or CH_3.

Scheme II.2



Because of the bulk of the methyl groups the palladium(II) will add to the center carbon[109,110] to give 2 and the carbons in 2 bonded to the hydroxyl or methoxyl groups contain no hydrogens to shift to give oxidative decomposition so only exchange and isomerization can occur. If R is H (water exchange), a label such as ^{18}O must be used. Of course, when R = CH_3, as in the present study, the exchange can easily be followed by the appearance of the $OC\underline{H}_3$ peak by ^1H NMR. An important feature of these exchanges is that when they are completely symmetrical as in the water exchange, $k_{-1} = k_{-1}'$ and the kinetics must measure only the rate expression for oxypalladation.[5] The oxypalladation steps are k_1 and k_1'. In the case where R = CH_3, k_{-1} might be *expected* to be very close to k_{-1}' since the groups are chemically very similar, but the relative rates are not known for certain. As previously discussed in chapter I, these studies are likely to shed some light on the oxypalladation step of the Wacker reaction.

The focus will be on the two reactions so far observed in studies of the oxidation of acyclic olefins by $PdCl_4^{2-}$ in water and methanol. Thus at low chloride concentrations a rate expression resembling equation II.1 will be expected to proceed

$$\text{Rate} = \frac{k_{ex}[PdCl_4^{2-}][\text{olefin}]}{[H^+][Cl^-]^2} \qquad \text{(II.1)}$$

through a mechanistic pathway similar to the Wacker oxidation of these substrates. At higher chloride conditions where oxidation is very slow, a non-oxidative exchange reaction which obeys the rate expression in equation II.2 has been observed. It

$$\text{Rate} = \frac{k_{ex}[PdCl_4^{2-}][\text{olefin}]}{[Cl^-]} \qquad \text{(II.2)}$$

might be expected that a similar reaction will occur in methanol with an analogous

mechanism.

B. Results

Control Experiments. Studies of the stability of 4-methyl-2-methyl-d_3-3-penten-2-ol in the presence of 0.10 M dichloroacetic acid in methanol indicated that the allyl alcohol was stable for up to 15 minutes without any observable change. However after 30 minutes under these conditions the formation of 2-methyl-d_3-4-methyl-1,3-pentadiene, a dehydration product, was observed. Under the acid conditions, $[H^+]$ = 0.0005 M - 0.01 M,[42] that the oxidation of ethene was previously found to obey the rate expression given by equation II.1, the starting allyl alcohol was stable in methanol for the time required to make the longest kinetic run. It was also stable indefinitely in the presence of 3.0 M LiCl.

Kinetics. The exchange and isomerization of 2-methyl-d_3-4-methyl-3-penten-2-ol in methanol catalyzed by Li_2PdCl_4 was first studied under reaction conditions which gave rapid ethene oxidation.[42] Data are given in Table II.1. Each run was plotted as a first order reaction in the allyl alcohol concentration. Correlation coefficients of greater than 0.96 were obtained indicating the reaction was indeed first order in 2-methyl-d_3-4-methyl-3-penten-2-ol. The kinetics are consistent with a expression given by equation II.1. Runs 1 - 4 indicate a first order dependence on $PdCl_4^{2-}$ concentration, while runs 2 and 7 - 9 show a first order inhibition by H^+, and runs 2, 5 and 6 a second order inhibition by Cl^-. The value of k_{ex} calculated assuming equation II.1 remains quite constant, considering the complexity of the rate expression. This confirms that equation II.1 is the correct rate expression for the reaction. The values of the isomerization rate constant were determined, using NMR, by the scrambling of the deuterium label. It was determined that the relaxation times for the CD_3 group in 2-methyl-d_3-4-methyl-3-penten-2-ol, (alcohol environment), and 2-methoxy-2-methyl-4-methyl-d_3-3-pentene, (vinyl environment), were similar, (T_1 = 0.623 ± 0.034 s for vinyl CD_3 and 0.710 ± 0.55 s for CD_3 in the

Table II.1. Rates of Exchange and Isomerization of 2-Methyl-d_3-4-methyl-3-penten-2-ol at Low Chloride Concentrations[a,b].

run	10^3 x $[CHCl_2CO_2H]$	10^5 x $[H^+]$[c]	$[Cl^-]$	10^3 x $[PdCl_4^{2-}]$	10^3 x k_{obsd},s^{-1}[d]	10^6 x k_{ex},M^2s^{-1}[e]
1	5.1	1.4	0.63	2.0	2.1(1.7)	5.9
2	5.1	1.4	0.60	4.0	4.0(3.8)	5.1
3	5.1	1.4	0.63	8.0	8.1(8.5)	5.7
4	5.1	1.4	0.61	16.0	16.0(16.2)	5.2
5	5.1	1.4	1.2	4.0	1.0(1.0)	4.9
6	5.1	1.4	0.32	4.0	18.0(16.5)	6.5
7	10.2	2.8	0.60	4.0	2.0(2.1)	5.1
8	20.4	5.6	0.63	4.0	0.97(0.90)	4.9
9	40.9	11.3	0.60	4.0	0.53(0.50)	5.4
					Average	5.5

[a] $[Cl^-] \leq 1.2$ M. [b] [allyl alcohol] = 0.171 M. [c] Calculated using a K_a of 4.0×10^{-7} for dichloroacetic acid.[28] [d] Values outside parentheses are those for exchange while values inside parentheses are those for isomerization. [e] Calculated assuming the rate expression is that given by equation II.1.

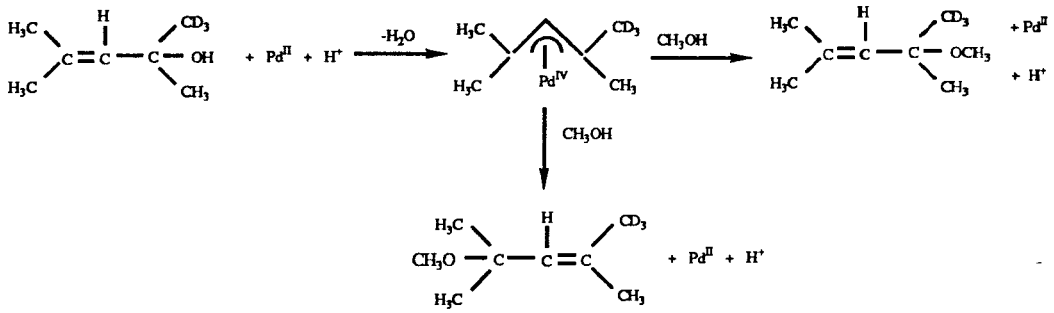
Table II.2. Rates of Exchange and Isomerization of 2-Methyl-d_3-4-methyl-3-penten-2-ol at High Chloride Concentration[a,b]

run	10^4 x $[Cl_2HCCO_2H]$	10^5 x $[H^+]$[c]	$[Cl^-]$	10^3 x $[PdCl_4^{2-}]$	10^4 x k_{obsd},s^{-1}[d]	10^5 x k_{ex},s^{-1}[e]
10	5.1	1.4	2.0	4.0	2.9(3.1)	1.5
11	5.1	1.4	1.5	4.0	3.6(4.0)	1.4
12	5.1	1.4	2.5	4.0	2.2(2.2)	1.4
13	10.2	2.8	2.0	4.0	3.0(2.9)	1.5
14	20.4	5.6	2.0	4.0	2.9(3.0)	1.5
15	5.1	1.4	2.0	8.0	5.7(5.0)	1.4
16	5.1	1.4	2.0	16.0	12.8(13.3)	1.6
17	5.1	1.4	2.0	2.0	1.4(1.7)	1.4
18	5.1	1.4	3.0	4.0	1.8(2.1)	1.4
					Average	1.4

[a] $[Cl^-] \geq 1.5$ M. [b] [allyl alcohol] = 0.171 M. [c] Calculated using a K_a of 4.0×10^{-7} for dichloroacetic acid.[28] [d] Values outside parentheses are those for exchange while values inside parentheses are those for isomerization. [e] Calculated assuming the rate expression is that given by equation II.2.

alcohol environment). This allowed for comparisons of the integrals of the peak areas. These results confirmed that the reaction is proceeding by the oxypalladation route shown in Scheme II.2. If exchange was twice as fast as isomerization, a mechanism involving Pd(IV) π-allyl species as shown in Scheme II.3,[130] could have been operative.[106]

Scheme II.3



The exchange and isomerization was next studied at $[Cl^-] \geq 1.5$ M. The kinetic data is given in Table II.2. Runs 14 - 17 show a first order dependence on $PdCl_4^{2-}$ concentration, while runs 10 - 12 and 18 demonstrate a first order inhibition by chloride. Runs 12 - 14 indicate that the reaction is zero order in acid. Finally the fact that the value of k_{ex} remains constant assuming a rate expression of the form of equation II.2, is further evidence that equation II.2 is the correct rate expression. Since the rates of isomerization are the same as the rates of exchange within experimental error, Scheme II.2 must be operative.

The data for the exchange of the ethyl ether of nondeuterated 1 given in Table II.3 clearly indicates a rate expression is the form of equation II.1. The first order dependence on $PdCl_4^{2-}$ concentration is shown by runs 19 - 21, and runs 19, 22, and

23, indicate a $1/[Cl^-]^2$ dependence. The first order acid inhibition is demonstrated by runs 19, 24 and 25.

Product Studies. The isomerization product, **1b**, in Scheme II.1 was identified by its ^1H and ^2H NMR spectra. At equilibrium integration of the resonances indicated a 50 - 50 mixture of the two isomers.

The oxidation, exchange and isomerization products for allyl alcohol, 3, and 4-methyl-3-penten-2-ol, 5, were studied under similar conditions, these results are reported in Table II.4, at low chloride concentrations, $[Cl^-] \leq 1.2$ M, and at high chloride concentrations, $[Cl^-] \geq 1.5$ M. Oxidation was the only process obtained for both unsaturated alcohols at low chloride concentrations. The oxidation product of allyl alcohol, 3, 3-methoxypropanal, $CH_3O\text{-}CH_2CH_2CHO$,[131] and of 4-methyl-3-penten-2-ol, 5, 4-methyl-4-methoxy-2-pentanone, $CH_3O(CH_3)_2CCH_2C(=O)CH_3$,[132] were identified by comparing their ^1H NMR spectra with those reported. At higher concentrations no oxidation was obtained, but exchange was observed for allyl alcohol, and both exchange and isomerization were obtained for 4-methyl-3-penten-2-ol in methanol. The exchange product from allyl alcohol, 3-methoxy-1-propene, $CH_3OCH_2CH{=}CH_2$,[133] the exchange product from 5, 4-methyl-4-methoxy-2-pentene, $CH_3O(CH_3)_2CCH{=}CHCH_3$,[134] as well as the isomerization product, 2-methyl-4-methoxy-2-pentene, $(CH_3)_2C{=}CHCH(CH_3)OCH_3$,[134] were also identified by comparing their ^1H NMR spectra with those reported. These oxidations proceeded very slowly, and were given up to 72 hours in order to accumulate enough products for analysis. They were carried out in the presence of quinone as there is great tendency to form palladium-π-allyl products.

Since allylic alcohols react with Pd(II) salts to form π-allyl species which could serve as catalysts,[135] the π-allyl from $PdCl_4^{2-}$ and nondeuterated 1 was prepared and its spectroscopic properties determined. It was then dissolved in methanol containing

Table II.3. Rates of Exchange and Isomerization of 2,4-Dimethyl-2-ethoxy-3-pentene in Methanol at Low Chloride Concentrations[a,b].

run	10^3 x $[CHCl_2CO_2H]$	10^5 x $[H^+]^c$	$[Cl^-]$	10^3 x $[PdCl_4^{2-}]$	10^4 x k_{obsd},s^{-1}[d]	10^6 x k_{ex},M^2s^{-1}[e]
19	5.1	1.4	0.60	4.0	10.1	1.3
20	5.1	1.4	0.60	12.0	28.5	1.2
21	5.1	1.4	0.60	16.0	35.7	1.1
22	5.1	1.4	1.2	4.0	2.5	1.2
23	5.1	1.4	0.3	4.0	42.8	1.4
24	10.2	2.8	0.60	4.0	5.5	1.4
25	20.4	5.6	0.63	4.0	2.9	1.5
					Average	1.3

[a] $[Cl^-] \leq 1.2$ M. [b] [allyl ether] = 0.171 M. [c] Calculated using a K_a of 4.0×10^{-7} for dichloroacetic acid.[28] [d] Values outside parentheses are those for exchange while values inside parentheses are those for isomerization. [e] Calculated assuming the rate expression is that given by equation II.1.

all the ingredients of a reaction mixture except Li_2PdCl_4. The reaction mixture was worked up in the usual fashion and it was found that the palladium(II)-π-allyl could be detected by ^1H and ^2H NMR. It could then be shown the π-allyl species was not present in any of the regular kinetic runs since no resonances due to this species were observed.

TABLE II.4. Distribution of oxidation and exchange products in methanol under varying chloride concentrations. [a]

substrate	$[Cl^-]$	oxidation product	%[b]	Exchange product	%[b]
$CH_2=CHCH_2OH$[c]					
	0.10	4	100.0	7	0.0
	0.50	4	98.5	7	0.5
	1.50	4	72.0	7	23.0
	2.50	4	1.0	7	98.0
	3.50	4	0.0	7	100.0
$(CH_3)_2C=CHCH(OH)CH_3$[d]					
	0.50	6	100.0	8	0.0
				9	0.0
	1.50	6	25.0	8	5.0
				9	70.0
	2.50	6	0.0	8	98.5
				9	1.5
	3.50	6	0.0	8	99.0
				9	1.0

4 = $CH_3OCH_2CH_2CHO$, 6 = $CH_3O(CH_3)_2CCH_2C(=O)CH_3$, 7 = $CH_3OCH_2CH=CH_2$, 8 = $CH_3O(CH_3)_2CCH=CHCH_3$, 9 = $(CH_3)_2C=CHCH(OCH_3)CH_3$. [a]$[PdCl_4^{2-}]$ = 0.05 M, $[H^+]$ = 2.82 x 10^{-5} M. [b]Determined as the percentage of total products obtained by ^1H NMR and GC. [c]Allyl alcohol was freshly distilled before oxidation studies, and concentrations were kept at [Allyl alcohol] = 0.10 M. [d]All runs with 4-methyl-3-penten-2-ol were done under similar conditions as those for allyl alcohol. Runs were done over a four day period at 25 °C in order to accumulate enough products, and worked up by extraction directly with ethyl ether.

C. Discussion

The results of this study clearly indicate conditions for conducting exchange reactions in methanol solvent while avoiding the complication of oxidation. At low chloride, under conditions analogous to the Wacker oxidation conditions in water, the only result is oxidation of both allyl alcohol, **3**, and 4-methyl-3-penten-2-ol, **5**, as shown in equations II.3 and II.4.

$$\underset{\mathbf{3}}{CH_2{=}CHCH_2OH} \xrightarrow[CH_3OH]{PdCl_4^{2-}} \underset{\mathbf{4}}{CH_3OCH_2CH_2CH{=}O} \qquad \text{(II.3)}$$

$$\underset{\mathbf{5}}{(CH_3)_2C{=}CHCH(CH_3)OH} \xrightarrow[CH_3OH]{PdCl_4^{2-}} \underset{\mathbf{6}}{CH_3O(CH_3)_2CCH_2C(CH_3)(=O)} \qquad \text{(II.4)}$$

On the other hand at high chloride concentrations exchange occurs readily without the complication of oxidation. As shown in equations II.5 and II.6 the

$$\underset{\mathbf{3}}{CH_2{=}CHCH_2OH} \xrightarrow[CH_3OH]{PdCl_4^{2-}} \underset{\mathbf{7}}{CH_3OCH_2CH{=}CH_2} \qquad \text{(II.5)}$$

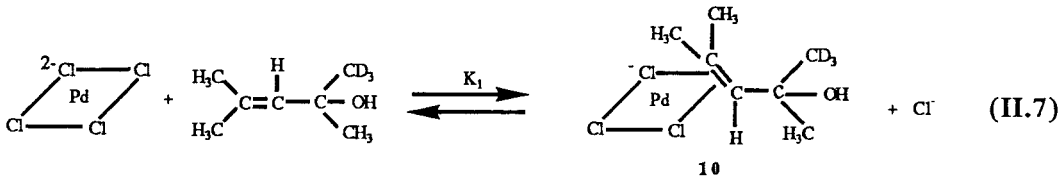
$$\underset{\mathbf{5}}{(CH_3)_2C{=}CHCH(CH_3)OH} \xrightarrow[CH_3OH]{PdCl_4^{2-}} \underset{\mathbf{8}}{CH_3O(CH_3)_2C{=}CH(CH_3)} \xrightarrow[CH_3OH]{PdCl_4^{2-}} \underset{\mathbf{9}}{(CH_3)_2C{=}CHCH(CH_3)OCH_3} \qquad \text{(II.6)}$$

products are allylic ethers. In the case of **5** the secondary isomerization occurs to give mainly **8** with smaller amounts of **8**.

It is almost certain that both oxidation and exchange proceed through oxypalladation intermediates analogous to **2** in Scheme II.2. The question is how does high chloride stabilize **2** from oxidative decomposition when one or more of the methyls are replaced by hydrogens. Chloride ion must be taking part in this stabilization. The only reasonable conclusion is that external chloride is inhibiting

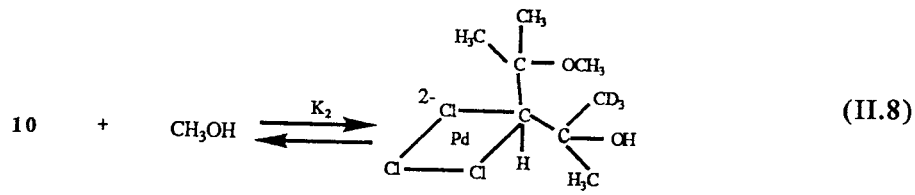
equilibrium that open up vacant or labile sites on the palladium(II), which can lead to oxidative decomposition. The oxidative decomposition by hydride shift believed to take place at low chloride and possible detailed mechanisms are discussed in the previous chapter and elsewhere.[136] The important point for the present discussion is that, at low chloride, a labile coordination site containing HOR is present which is believed necessary for hydride shift.[127,128]

The mode of oxypalladation at low [Cl^-] is changed from one that requires two chlorides to dissociate from the coordination sphere of palladium(II) to one at high [Cl^-] that requires only one chloride to dissociate so this is further evidence that high chloride is changing the entire mechanism of the palladium(II) catalysis. The kinetics are consistent with trans methoxypalladation. Since olefin activation by π-complex formation is always a necessary step in palladium(II) catalysis, the first power chloride inhibition must result from the equilibrium shown in equation II.7. Since the kinetics only allow for one species to be coordinated to palladium(II),



10 (II.7)

the methanol must attack from outside the coordination sphere of the palladium(II) as shown in equation II.8. The replacement of HOR by Cl^- to give **10** stabilizes the



(II.8)

oxypalladation adduct against the oxidative decomposition by hydride shift, see equations I.27 to I.32. Thus **10** can only reverse the oxypalladation step to give exchange. The stabilization of the intermediate methoxypalladation adduct by high chloride has the secondary effect of changing somewhat the mode of addition. Of

course it is possible that the stereochemistry of addition of methanol at low chloride is also trans[100,101] but the removal of the second chloride to give a neutral palladium(II) species may make the addition more facile under low [Cl^-] conditions. The stability of palladium(II) oxypalladation adducts containing strongly coordinating neutral groups is well documented.[110a,b] Thus olefins containing heteroatoms such as nitrogen and sulfur have long been known to form stable oxypalladation adducts[137] as have chelating diolefins.[79,102,138,139] Some interesting mechanistic studies have been carried out using methoxypalladation adducts of chelating olefins containing nitrogen donor atoms.[140] In another study it was demonstrated that a palladium(II)-π-complex containing η^5-C_5H_5 and phosphine ligands was converted to a stable methoxypalladation adduct by trans attack of methanol.[141] No doubt the reason for the stability of these adducts results from the fact that the strongly complexing ligands prevent formation of labile coordination sites on palladium(II) and thus inhibit the oxidative decomposition by β-hydrogen transfer shown in equation I.27. Thus there is kinetic evidence that vacant coordination sites are required for the decomposition of oxypalladation intermediates[127] and there is also evidence that such sites are required for decomposition of platinum(II) alkyls.[128] In the present study the palladium(II) species have been stabilized to the extent that it does not oxidatively decompose, but still undergoes demethoxypalladation at such a rate that the intermediate adduct does not build up and the reaction becomes catalytic in palladium(II).

The success of the diamine complexes of palladium(II) acetate, is, no doubt, also due to the stabilization of the oxypalladation intermediate by the strongly complexing diamine groups.[110a,b] The kinetic results at low chloride give a clue as to possible modes of methoxypalladation under these conditions. Of particular interest is the fact that the rate expression for exchange is identical to that found for oxidation of

ethene in methanol. The same rate expression is also found for the oxidation of acyclic olefins in water including allyl alcohol and substituted allyl alcohols. It is universally agreed that the square chloride inhibition results from the equilibrium shown in equation II.7 to form the reactive π-complex followed by a second equilibrium to replace a Cl^- by HOR as shown in equation I.22.[125]

The oxidation products from allyl alcohol at low chloride deserve brief comment. The only product was 3-methoxypropanal, equation II.3, which arose from addition of palladium(II) to the center carbon as shown in equation II.9 followed by a hydride

$$\underset{\mathbf{3}}{CH_2{=}CHCH_2OH} \xrightarrow[CH_3OH]{Pd(II)} H^+ + \underset{\substack{\\ Pd(II)}}{CH_3OCH_2CHCH_2OH} \xrightarrow[CH_3OH]{-Pd(0)} \underset{}{CH_3OCH_2CH_2CH(=O)} \qquad \textbf{(II.9)}$$

shift from the alcohol carbon. A hydride shift from the carbon containing the CH_3O- group would have given$(CH_3O)_2CHCH_2CH_2OH$ which was not observed. Apparently hydride shift from an alcoholic carbon is much preferred over a shift from an ether carbon a result which is not too surprising. Secondly, the oxidation of allyl alcohol in water gave a 12 - 15% yield of α-hydroxy acetone, (acetol),[91] which would correspond to the dimethyl ketal in methanol. As shown in equation

$$\mathbf{3} + Pd(II) + CH_3OH \xrightarrow{-H^+} \underset{\mathbf{11}}{Pd(II)\text{-}CH_2CH(OCH_3)CH_2OH} \xrightarrow{-Pd(0)} \underset{\mathbf{12}}{CH_3C(OCH_3)_2CH_2OH} \qquad \textbf{(II.10)}$$

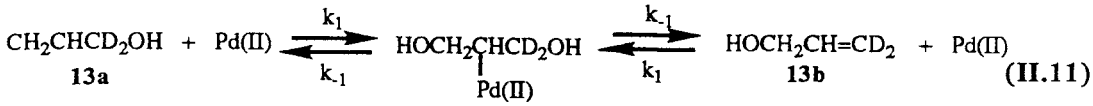
II.10 the ketal would be formed by addition of palladium(II) to the end carbon to give **11** followed by oxidative decomposition to give **12**. The hydroxyl group is known to direct palladium(II) to the carbon next to the carbon containing the hydroxyl in hydroxypalladations in aqueous solution.[111b,91] For allyl alcohol the preference for center carbon, equation II.9, to end carbon, equation II.10, is 2.5 to one. Since **12** is not detected in methanol, the preference must be higher. This is

also not surprising since methanol has a lower dieletric constant than water and is a poorer solvating solvent so the directing effect of the O-H····Cl-Pd hydrogen bonding interaction might be expected to be stronger in methanol than in water. On the other hand the differences in rate between the alcohol, **1a**, and its ethyl ether is a little more than four with the alcohol being the faster. This result suggests that the hydrogen bonding effect does not greatly increase the value of K_1 in equation II.7 or, if it does, this effect is counterbalanced by a slowing of a later process in the reaction scheme. It could be that stabilization of the π-complex slows the rate of oxypalladation, equation I.24.

It is surprising that the absolute rate of exchange of **1a** at low chloride concentrations is so fast. In fact it is almost exactly the same as the corresponding rate of oxidation of ethene in methanol.[42,142] The increased substitution on the double bond would have been expected to decrease the rates of oxypalladation. Thus, in aqueous solution 2-buten-1-ol, which is much less substituted than **1a**, is oxidized at a rate 0.025 times that of ethene.[111b] The reason for the high reactivity of **1a** towards methoxypalladation is unknown but it does indicate that these highly substituted olefins are suitable models for their less hindered counterparts. Thus these tetrasubstituted allylic alcohols have the potential to allow the study of the metallation reaction in other systems without the complicating factors of steps such as oxidative decomposition.

The last part of this chapter will focus on the acid inhibition controversy discussed in Chapter I. The validity of extrapolating the results of these studies to the conditions of the aqueous olefin oxidation has been discussed.[106]

Previously equilibrium hydroxypalladation was tested by studying the oxidation and isomerization of allyl-1,1-d_2-alcohol (**13a**). If hydroxypalladation is reversible **9a** should be isomerized into allyl-3-3-d_2-alcohol (**13b**) via equation II.11. In fact *no*

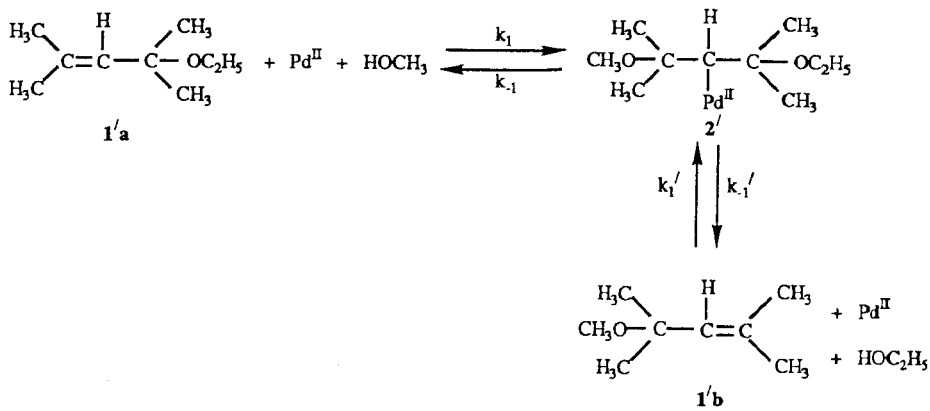


13a 13b (II.11)

isomerization was observed, indicating that hydroxypalladation is not an equilibrium process in this system but rather the slow step of the oxidation.[86b]

The reaction sequence shown in Scheme II.4 provides, in principle, another

Scheme II.4



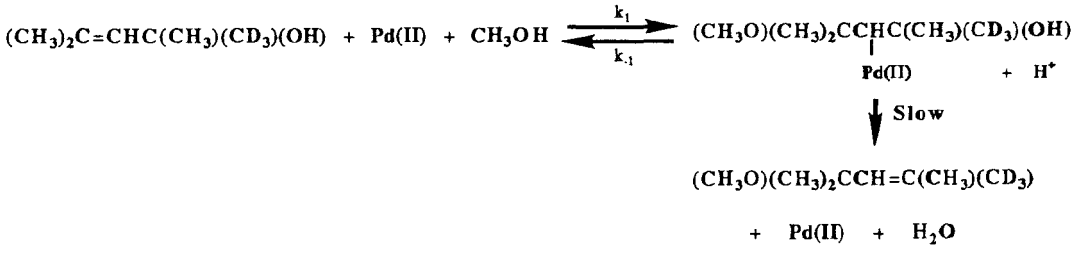
means of choosing between the two routes. As opposed to Scheme II.2, the two oxygen containing groups in 2 have about the same tendency to eliminate, $k_{-1} = k_{-1}'$ and the oxypalladation step becomes the rate determining step for both exchange and isomerization because exchange occurs in half the time that oxypalladation occurs. This is the reason no proton inhibition appears in equation II.2 for the exchange and isomerization in aqueous solution at high chloride. If this condition is met the proton inhibition cannot result from the equilibrium shown in equation I.25. In other words, if equation I.25 was the reason for the proton inhibition in the oxidation, the rate expression for the exchange would be given by equation II.12. The only

$$\text{Rate} = \frac{k_{ex}[PdCl_4^{2-}][\text{olefin}]}{[Cl^-]^2} \qquad \text{(II.12)}$$

reasonable conclusion is that a rate expression such as equation II.1 for a symmetrical exchange indicates that proton release occurs before the oxypalladation step takes place.

Of course the alcohol to ether exchange is not a completely symmetrical one as shown below. It is possible that the reaction follows Scheme II.5, involving

Scheme II.5



equilibrium oxypalladation followed by slow elimination of the hydroxyl group. One piece of evidence that Scheme II.5 is not operative is the fact that at high chloride, where non-oxidative exchange is taking place, there is no proton inhibition indicating the equilibrium shown in Scheme II.5 is not operative. However, this evidence is not conclusive since the modes of oxypalladation under the two sets of conditions are not exactly the same.

In order to remove any uncertainty concerning pre-equilibrium processes, the exchange of the ethyl ether of the nondeuterated analog of **1a** in methanol was studied at low chloride. The rate expression is again of the form of equation II.1. This exchange is for all practical purposes chemically symmetric, confirming that the proton inhibition must result from a pre-equilibrium such as that shown in equation

I.25. This study thus provides further support for the oxypalladation sequence shown in equations I.23 and I.24. What is now needed is similar evidence in aqueous solution under the conditions of the Wacker process and stereochemical evidence to support the kinetic results. This study as well as at least one other has demonstrated that the mode of oxypalladation can change with chloride concentration even in the same solvent so interpretation of stereochemical data must be done very carefully. We believe that stereochemical data for the Wacker chemistry is valid only under conditions of the rapid olefin oxidation (low [Cl^-]) and with olefins whose oxidation kinetics obey equation II.1.

D. Experiment

Starting Materials. The palladium(II) chloride was purchased from Aesar. The methanol, HPLC grade from Aldrich Chemicals (Sureseal), was dried further with trimethyl orthoformate. All other chemicals were of reagent grade. Stock solutions of the following compositions were prepared: 0.2 M in Li_2PdCl_4, 2.0 M in LiCl, 2.0 M in dichloracetic acid, 3.0 M in $LiClO_4$. Reaction mixtures were prepared by diluting these stock solutions.

Standardization of $PdCl_4^{2-}$ Stock Solution. From an unstandardized stock solution of 0.2 M Li_2PdCl_4 in water was pipetted 10 mL of solution. This was diluted to 30 mL of solution with deionized water, followed by 20 mL of 10 % HCl solution. To this solution was added excess amounts of 1% dimethylglyoxime in ethanol, and the mixture allowed to stand for 30 minutes. A golden precipitate appeared. A sintered glass funnel was dried to constant weight at 150 °C, and used for filtering this product, which was also dried to constant weight at 150 °C. The yield of product obtained after final weighing was 0.6267 g, which is equal to 0.00186 moles. Upon conversion the molarity of stock solution was determined to be 0.186 moles/liter in palladium concentration.[150]

Kinetics. The rate of exchange and isomerization were studied simultaneously on a 25 mL scale by working up 5 mL portions of the reaction mixture at various times. The 5 mL aliquots were pipetted into 25 mL of CH_2Cl_2 which was then washed with 2-25 mL portions of water followed by 25 mL of saturated sodium bicarbonate and again with 25 mL of distilled water. The organic layer was the dried over anhydrous $MgSO_4$ and evaporated slowly at room temperature. ^1H and ^2H NMR spectra were obtained for each workup. NMR spectra were recorded on a Varian 300 MHz VXR 300 instrument at 20°C. The rate of exchange was studied using ^1H NMR, by measuring the increase in the areas of the OCH_3 singlet at 3.25 ppm and the CH singlet at 5.10

ppm corresponding to 2-methoxy-2-methyl-4-methyl-d_3-3-pentene, against the decrease in the area of the CH singlet at 5.34 ppm corresponding to 2-methyl-d_3-4-methyl-3-pentene-2-ol. The isomerization was followed using ^2H NMR, by measuring the increase in the area of the peak at 1.2 ppm corresponding to 2-methoxy-2-methyl-d_3-4-methyl-3-pentene against the decrease in the area of the peaks at 1.6 to 2.0 ppm corresponding to the starting alcohol.

The data for isomerization were treated as a first order reaction approaching equilibrium.[143] A plot of log (50% - % isomerized) vs time was made on semilog paper and the half-life read off at the 25% point. Since the value for the equilibrium constant for the isomerization is equal to 1, the rates for the forward and reverse reactions are identical and the value of the slope of the plot of ln (50% - % isomerized) vs time = $-2k_{obsd}$.

The stock reaction mixture was prepared in a 25 mL volumetric flask. The temperature was kept constant at 25 ± 0.1°C in a constant temperature water bath. Quinone was added to each run to prevent the formation of palladium-π-allyl species and as the reoxidant for atomic palladium(0). For kinetic runs at $[Cl^-] \leq 1.2$ M, the ionic strength, μ, was maintained at 2.0 M with the addition of the appropriate number of moles of $LiClO_4$. The allyl alcohol was kept at 0.171 M for each run. [Pd(II)] was varied between 0.002 M and 0.2 M, $[Cl^-]$ between 0.1 M and 3.0 M, and $[H^+]$ between 0.00001 M and 0.0002 M. H^+ was added in the form of dichloroacetic acid, which is reported to have a K_a of 4×10^{-7} in methanol.[144]

Product Identification. The isomerization product **1b** was identified by comparison of its spectra with that of the non-deuterated analog reported in the literature.[145] The products from **4** and allyl alcohol at low and high chloride were identified by working up the reaction mixtures and comparing their ^1H NMR spectra with those reported in the literature. In the case of exchange and isomerization of **4**

at high [Cl^-], the two products, **5** and **6**, were separated by column chromatography using a 2 cm x 6 cm silica gel column with 20:80 methylene chloride: petroleum ether as eluant. The 20 mL samples that were collected were evaporated at room temperature. The fractions were identified by NMR. Their relative amounts were determined from a reaction mixture before separation.

Preparation of 2-Methyl-d_3-4-methyl-3-penten-2-ol.[146] To 100 mL of 1.0 M CD_3MgI in anhydrous ether was added 9.0 g (0.09 moles) of mesityl oxide, previously dried over anhydrous $MgSO_4$, under a flow of nitrogen. This was stirred for one hour and then neutralized with 100 mL of 5% HCl. It was stirred until all the precipitate was dissolved. The ether layer was separated and the aqueous layer neutralized with saturated $NaHCO_3$. It was then extracted with 4 x 50 mL portions of ether which were combined and washed with saturated Na_2SO_4, dried over anhydrous $MgSO_4$. The solvent was air evaporated. Weight = 6.4 g, Yield = 61%. The product was identified by comparing its ^1H NMR spectra with that of its non-deuterated analog reported in the literature.[147]

300 MHz ^1H NMR ($CDCl_3$): δ = 1.31 (s, 3H), 1.71 (s, 3H), 1.87 (s, 3H), 5.34 (s, 1H). ^2H NMR ($CHCl_3$) 1.30 (s,3D). ^{13}C NMR ($CDCl_3$): δ = 132, 134, 71, 31, 27, 19.

Preparation of 4-Methyl-3-penten-2-ol.[148] 5.7 g (0.06 mole) of mesityl oxide was dissolved in 150 mL of 0.4 M $CeCl_3$ in methanol. After stirring for ten minutes at room temperature 2.3 g (0.06 mole) of $NaBH_4$ was added rapidly. This was allowed to stir for an additional five minutes and then hydrolyzed with 150 mL of cold saturated ammonium chloride. This was extracted with methylene chloride, dried over anhydrous $MgSO_4$ and the solvent air evaporated. Yield = 4.2 g (70%).

300 MHz ^1H NMR ($CDCL_3$): δ = 1.13 (d, 3H), 1.61 (s, 3H), 1.65 (s, 3H), 2.79 (s, OH), 4.45 (q, 1H), 5.13 (d, 1H).[6] ^{13}C NMR ($CDCl_3$): δ = 134, 130, 65, 26, 24, 18.

Preparation of 2,4-Dimethyl-2-ethoxy-3-pentene. A 0.44 g sample of

palladium(II) chloride (0.0025 moles), and 0.32 g of lithium chloride (0.0075 moles) were dissolved in anhydrous ethanol. After all the $PdCl_2$ dissolved excess anhydrous $MgSO_4$ was added followed by 3.0 g of 2,4-dimethyl-3-penten-2-ol (0.0026 moles). This was allowed to stir for 48 hrs. at room temperature in a capped Erlenmeyer flask. After adding 25 mL of $CHCl_3$ and washing with four 25 mL portions of distilled water, the organic phase was dried ($MgSO_4$), and evaporated to give 2.5 g of 2,4-dimethyl-2-ethoxy-3-pentene (0.0018 moles), 69% yield. 300 MHz ^1H NMR ($CDCl_3$): δ = 1.12 (t, 3H), 1.25 (s, 6H), 1.66 (s, 3H), 1.76 (s, 3H), 3.30 (q, 2H), 5.04 (s, 1H). ^{13}C NMR

($CDCl_3$) δ = 18.0, 19.5, 23.5, 24.5, 58, 75, 130, 133.

Preparation of Dichloro(1,1,3,3-Tetramethyl allyl) Palladium(II).[149] 1 g of 2,4-dimethyl-3-penten-2-ol was dissolved in 25 mL of 0.20 M Li_2PdCl_4 in dry methanol. This was stirred for 10 hours. 50 mL of methylene chloride was added and the resulting solution washed with 4 x 50 mL portions of saturated sodium carbonate. The organic phase was dried over anhydrous $MgSO_4$ and evaporated under vacuum. Golden yellow crystals were obtained. Weight = 0.56 g, Yield = 40%. mp (decomposition) = 123°C. 300 MHz ^1H NMR ($CDCl_3$): δ = 1.5 (m, 12H), 4.75 (s, 1H).^{13}C NMR ($CDCl_3$): δ = 28, 31, 132, 133, 134.

CHAPTER III

PALLADIUM(II)-CATALYZED EXCHANGE AND ISOMERIZATION OF A TETRASUBSTITUTED ALLYLIC ALCOHOL IN AQUEOUS ACID SOLUTION - A NEW MECHANISTIC PROBE FOR WACKER CHEMISTRY

A. Purpose

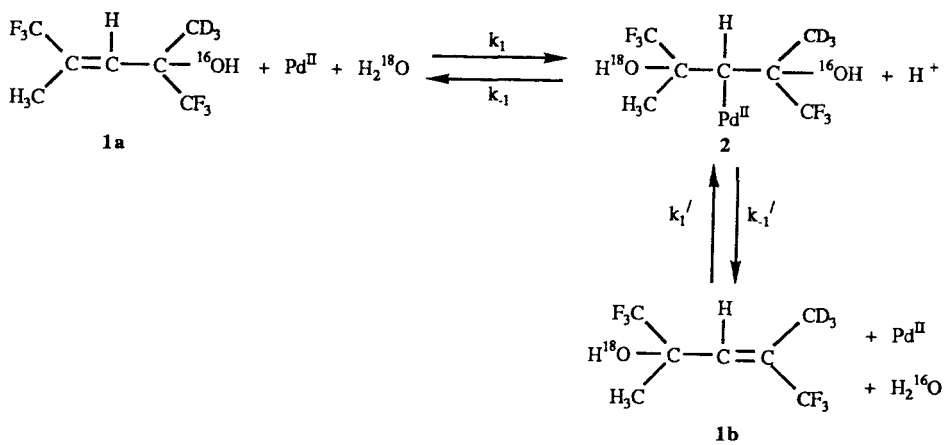
In prior studies of the mechanisms of palladium(II) catalyzed reactions the focus has been on the complete reaction rather than on its component parts.[85] This of course, is necessary since in practically all cases the intermediate steps cannot be separated and studied independently. Most palladium(II) reactions of olefins involve the addition of palladium(II) and nucleophiles to double bonds (palladation) followed by decomposition, usually oxidative. It is difficult to interpret the kinetics unambiguously in such complicated catalytic systems. In the Wacker process for oxidizing ethene to acetaldehyde, discussed extensively in Chapter I, the rate expression is dependent on $[PdCl_4^{2-}]$ and [olefin] to the first order, inverse first order in $[H^+]$, and inverse second order in $[Cl^-]$. This is consistent with (a) cis addition by coordinated hydroxyl in the slow step,[86a,89,90a] or (b) trans attack by external water in an equilibrium step[125] followed by rate determining decomposition of the adduct formed.

The strategy employed involves a look at the kinetics of a very simple reaction

for which the rate determining step is known to be hydroxypalladation. This reaction is the isomerization and water exchange of an allylic alcohol. In addition this alcohol cannot have hydrogens at the terminal carbons or else it will undergo oxidation by Wacker chemistry to give carbonyl products. Thus a tetrasubstituted allylic alcohol is required. It was found that 1,1,3,3-tetramethyl allylic alcohol was hydrolytically unstable under the acid conditions of the Wacker reaction, but the substitution of two of methyls by trifluoromethyl groups gave the required hydrolytic stability to the allylic alcohol used in these studies, 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol.[159]

The reason the rate determining step for the water exchange and isomerization of this olefin is hydroxypalladation can be seen from the examination of Scheme III.1. In a completely symmetrical exchange such as this, the value of $k_1 = k'_1$ and

Scheme III.1



$k_{-1} = k'_{-1}$. Thus half the time that **1a** is converted to **2**, **2** reverts to **1a** and half the time it goes to **1b**. The rate depends only on the formation of **2** and not on its equilibrium concentration.

As discussed in Chapter I the mode of oxypalladation and stability of the

intermediate oxypalladation adduct depends on the ligands around the palladium. An example of a relatively stable intermediate is **2** in Scheme III.1. Once the mode of oxypalladation by $PdCl_4^{2-}$ has been defined, the effect of monodentate ligands containing nitrogen will be investigated. The remaining monodentate ligands will be chloride for this study.

B. Results

All kinetic runs were carried out at 25°C. Preliminary control experiments revealed that there was no oxidation evident over 24 hours under all reaction conditions. There was no acid or chloride catalyzed isomerization observed in the absence of $PdCl_4^{2-}$. Under all reaction conditions dehydration of the alcohol species was not observed.

Exchange and isomerization data at chloride concentrations less than or equal to 1 M, with $PdCl_4^{2-}$ as catalyst, are given in Table III.1. The values of k_{obs} were determined as a first order dependence in the decrease of the starting allylic alcohol with time, and straight lines were obtained reflecting a first order dependence of the rate on the concentration of starting allylic alcohol. A plot of k_{obs} vs $[PdCl_4^{2-}]$ for runs 1, 2, 4, 5, 10 and 11 gave a straight line, all other variables remaining constant. This showed a first order dependence of the rate on the concentration of $PdCl_4^{2-}$ catalyst. An acid inhibition term was obtained from the plots of $[H^+]$ in runs 3, 5 to 7 and 11 vs k_{obs}. A squared chloride inhibition term was also determined from plots of $[Cl^-]$ in runs 3 to 5 and 8 to 9. The rate expression obtained under these conditions, equation III.1, resembled the Wacker rate expression for the oxidation of

$$\text{Rate} = \frac{k_i[PdCl_4^{2-}]\,[C_7H_5D_3F_6O]}{[H^+]\,[Cl^-]^2} \qquad \textbf{(III.1)}$$

acetylene in aqueous acid solution.[86a] The values of k_i were calculated using equation III.1.

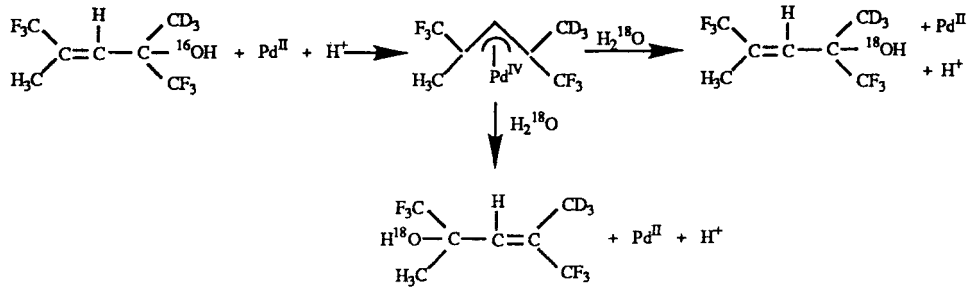
The ^{18}O exchange rate constants for two sets of reaction conditions is also given in Table III.1. The value of k_{ex} also calculated on the basis of equation III.1, is the same as the value of k_i. This result requires that Scheme III.1 rather than Scheme III.2 be operative. Scheme III.2 shows a mechanistic pathway in which the

Table III.1. Rates of Isomerization and ^{18}O Exchange of 2-Methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol at Low Chloride Concentrations.[a]

run	$[PdCl_4^{2-}]$	$[H^+]^b$	$[Cl^-]^c$	$10^6 \times k_{obsd}$, s^{-1}	$10^5(k_i$ or $k_{ex})$,[d] $M^2 s^{-1}$
			Isomerization		
1	0.007	0.05	0.5	7.7	1.4
2	0.015	0.05	0.5	13	1.1
3	0.008	0.10	0.25	15	1.2
4	0.016	0.10	1.0	1.3	0.81
5	0.008	0.05	0.5	6.0	0.92
6	0.008	0.15	0.5	2.1	0.98
7	0.008	0.20	0.5	1.5	0.91
8	0.008	0.10	0.20	23	1.2
9	0.008	0.10	0.75	1.7	1.2
10	0.004	0.10	0.50	1.5	1.0
11	0.032	0.40	0.50	3.5	1.1
				Average	1.1
			^{18}O Exchange		
12	0.008	0.10	0.5	3.6	1.1
13	0.008	0.05	1.0	1.5	0.92

[a] $[Cl^-] \leq 1.0$ M; all runs are in aqueous solution at 25 °C; quinone (0.10 M) added to all runs to prevent the formation of Palladium(0). In all runs initial $[C_7H_5D_3F_6O]$ = 0.044 M. For all runs in which $[H^+] + [Cl^-]$ was less than 2.0 M, $LiClO_4$ was added to bring the ionic strength (μ) to 2.0 M. [b] Added as $HClO_4$. [c] Added as LiCl. [d] k_i were calculated for runs 1 - 13 assuming the rate expression given in equation III.1 is operative and $[PdCl_4^{2-}]$, $[H^+]$ and $[Cl^-]$ are constant for each run.

Scheme III.2



intermediate is a palladium(IV) species.[152,153] If Scheme III.2 was operative, then each time isomerization occurs, two exchanges would be possible. In other words $k_{ex} = 2k_i$. The fact that k_i remained constant over a wide range of $[PdCl_4^{2-}]$, $[Cl^-]$ and $[H^+]$ indicates that equation III.1 is the correct expression with a value of 1.1 x 10^{-5} M^2s^{-1} for k_i. It is note worthy that the rate expression holds up to $[Cl^-] \leq$ 1.0 M, well into the Wacker oxidative conditions for the oxidation of ethene in water.

Isomerization data for chloride concentrations greater than or equal to 2.0 M are given in Table III.2. A plot of k_{obs} vs $[PdCl_4^{2-}]$ for runs 14, and 19 to 21 gave a straight line indicating a first order dependence of the rate on palladium(II) concentration. There was no dependence of the rate of reaction on the concentration of H^+ as demonstrated by the variation of k_{obs} vs $[H^+]$ for runs 14, 17, 18, 24 and 25. Only a single chloride inhibition term was obtained, when k_{obs} was plotted against the chloride concentrations for runs 14 to 16, and 22 to 23. This results in the rate expression show in equation III.2. The values for k_i were calculated using equation III.2. The fact that k_i remains constant over a wide range of $[PdCl_4^{2-}]$ and $[Cl^-]$ indicates that equation III.2 is in fact the correct expression

Table III.2. Rates of Isomerization of 2-Methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol at High Chloride Concentrations.[a]

run	$[PdCl_4^{2-}]$	$[H^+]$[b]	$[Cl^-]$[c]	$10^6 \times k_{obsd}$, s^{-1}	$10^3 k_i$, s^{-1}
14	0.016	0.05	2.0	8.4	1.1
15	0.016	0.05	2.5	6.7	1.1
16	0.016	0.05	3.0	5.5	1.0
17	0.016	0.10	2.0	8.3	1.0
18	0.016	0.15	2.0	8.4	1.1
19	0.008	0.05	2.0	4.1	1.0
20	0.032	0.05	2.0	17	1.1
21	0.064	0.05	2.0	34	1.1
22	0.016	0.05	4.0	4.4	1.1
23	0.016	0.05	3.5	5.1	1.1
24	0.016	0.20	2.0	8.2	1.0
25	0.016	0.40	2.0	8.4	1.1
				Average	1.1

[a] $[Cl^-] \geq 2.0$ M; all runs are in aqueous solution at 25 °C; quinone (0.10 M) added to all runs to prevent the formation of Palladium(0). In all runs initial $[C_7H_5D_3F_6O] = 0.044$ M. [b] Added as $HClO_4$. [c] Added as LiCl. [d] k_i were calculated for runs 14 - 25 assuming the rate expression given in equation III.2 is operative and $[PdCl_4^{2-}]$ and $[Cl^-]$ are constant for each run.

$$\text{Rate} = \frac{k_i[PdCl_4^{2-}]\,[C_7H_5D_3F_6O]}{[Cl^-]} \qquad \text{(III.2)}$$

with a value of $1.1 \times 10^{-3}\ s^{-1}$ for k_i. This expression holds for $[Cl^-] \geq 2.0$ M.

Table III.3 gives the rates of isomerization of 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol in water with $PdCl_3Py^-$ as catalyst.[162] The maximum solubility of this catalyst in water at 25°C was 0.1 M. Control experiments indicate no observable reaction, isomerization or oxidation, in the absence of the catalyst. No oxidation took place at any time over a 24 hour period in the presence of the catalyst. A single order chloride inhibition of the rate of reaction was obtained from plots of k_{obs} vs chloride concentration for runs 26 to 30. When k_{obs} was plotted against $[H^+]$ for runs 27 to 28, and 30 to 32, the acid concentration had no effect on the rate. A first order dependence of rate on $[PdCl_3Py^-]$ was obtained from plots of k_{obs} vs palladium(II) concentration for runs 28 to 31, and 33, and lead to the rate expression given in equation III.3, and indicate that the intermediate for

$$\text{Rate} = \frac{k_i[PdCl_3Py^-][C_7H_5D_3F_6O]}{[Cl^-]} \qquad \text{(III.3)}$$

the isomerization with $PdCl_3Py^-$ as catalyst is similar to the one proposed for the similar reaction observed for 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol with $PdCl_4^{2-}$ as catalyst at chloride concentrations greater than 2.0 M in aqueous acid solution.

Table III.3. Rates of Isomerization of 2-Methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol with $PdPyCl_3^-$ as Catalyst.[a]

run	$[PdPyCl_3^-]$	$[H^+]$[b]	$[Cl^-]$[c]	$10^6 \times k_{obsd}, s^{-1}$	$10^5 \times k_i, M^2s^{-1}$[d]	$10^4 \times k_i, {}^e s^{-1}$
26	0.01	0.40	0.20	9.84	1.6	2.0
27	0.01	0.40	0.40	5.60	3.6	2.2
28	0.01	0.40	0.60	3.16	4.6	1.9
29	0.02	0.40	0.80	5.32	6.8	2.1
30	0.04	0.20	1.0	5.65	2.8	1.4
31	0.08	0.80	0.60	25.6	9.2	1.9
32	0.08	0.60	0.60	25.1	6.8	1.9
33	0.005	0.20	0.20	3.92	6.3	1.6
				Average	5.2 ± 4.0	1.6

[a]All runs are in aqueous solution at 25 °C; quinone (0.10 M) added to all runs to prevent the formation of palladium(0); in all runs, initial $[C_7H_5D_3F_6O]$ = 0.044 M. [b]Added as $HClO_4$. [c]Added as LiCl. [d]k_i were calculated for runs 26 to 33 assuming that a rate expression similar to the one given in equation III.1 was operative, with $PdCl_3Py^-$ as catalyst, and $[PdCl_3Py^-]$, $[H^+]$ and $[Cl^-]$ are constant for each run. [e]k_i were calculated similarly assuming that the rate expression given in equation III.3 was operative, and $[PdCl_3Py^-]$ and $[Cl^-]$ were constant for each run. Ionic strength was kept constant at 2.0 M using $LiClO_4$.

C. Discussion

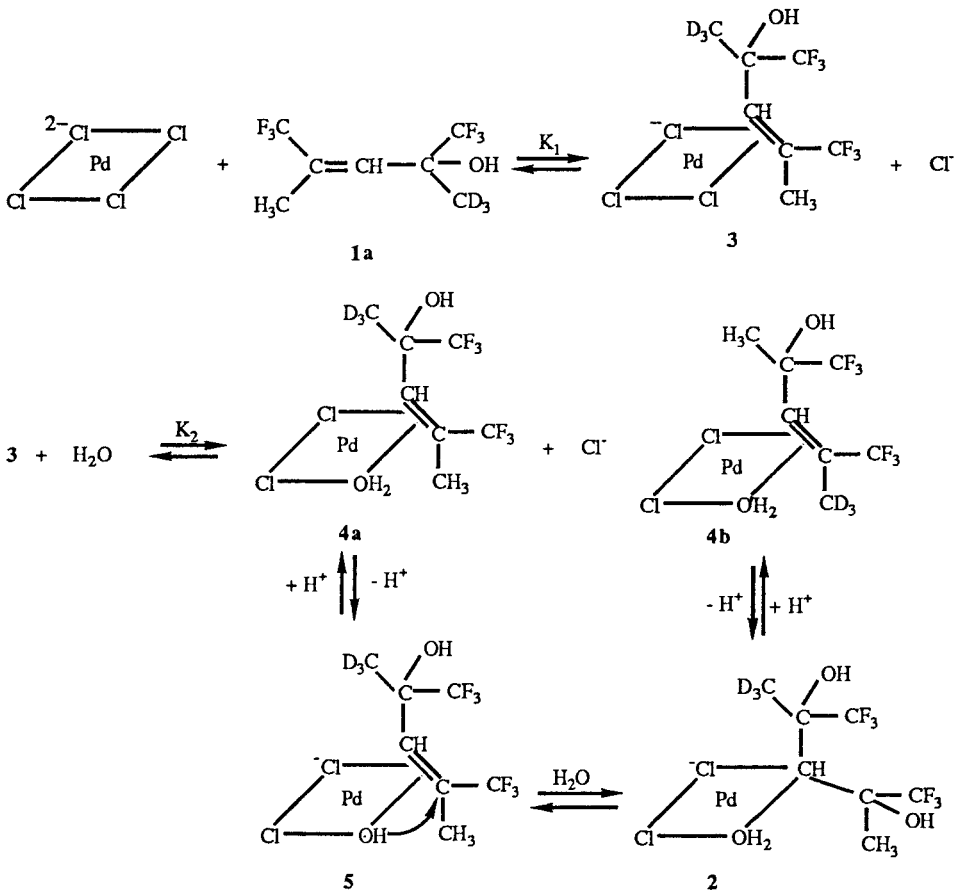
The kinetics for the equilibrium outlined in Scheme III.1 were studied under Wacker reaction conditions[91] at various chloride concentrations, with $PdCl_4^{2-}$ and $PdCl_3Py^-$ as catalysts. The results reveal that the rate expression for the conditions under which oxidation of ethylene is dominant, namely 0.2 M < $[Cl^-]$, $[H^+]$ < 1.0 M, and 0.002 M < [Pd(II)] < 0.2 M,[91] is that as described in equation III.1. This has some implications on the proposed mechanisms for the oxidation of ethylene in aqueous solution, Wacker oxidation, with $PdCl_4^{2-}$ as catalyst.

This study is aimed at probing the process of hydroxypalladation via a palladium(II) intermediate, which is similar to that investigated for the Wacker oxidation system in water[86a] and methanol.[154] It has been shown however that a pathway going through a palladium(IV) intermediate is possible,[130,152] and so exchange studies were done to determine which pathway was active. Scheme III.1 summarizes the pathway via a palladium(II) intermediate. If this scheme was active then the rate of isomerization would be expected to be equal to the rate of exchange with ^{18}O. On the other hand if the path described in Scheme III.2 was proceeding then each time isomerization occurred there would be two exchanges, making exchange appear twice as fast as isomerization. The results indicate that the rate of exchange is equal to the rate of isomerization eliminating the path described by Scheme III.2. The isomerization and exchange process under investigation is thus proceeding through a palladium(II) species similar to that for the oxidation of ethylene in water under Wacker conditions.[125]

Table III.1 summarizes the results under Wacker oxidation conditions. At low chloride concentrations, $[Cl^-] \leq 1.0$ M, with $PdCl_4^{2-}$ as catalyst the rate expression obtained resembled that of the Wacker rate expression for the aqueous oxidation of ethylene.[86a,89] As summarized in Scheme III.3 this would require that both systems

go through a similar mechanism. The first two steps will hence be similar to the equilibriums in equations I.21 and I.22, in which the π-complex, 3, is formed giving up a coordinated chloride, followed by the replacement of a second coordinated

Scheme III.3



chloride by solvent water giving **4a**. This accounts for the squared chloride inhibition terms in the rate expression. For the third step of this mechanism, it cannot be an equilibrium hydroxypalladation step as proposed by Bäckvall for the Wacker oxidation of ethylene, but must be an equilibrium loss of a proton from the

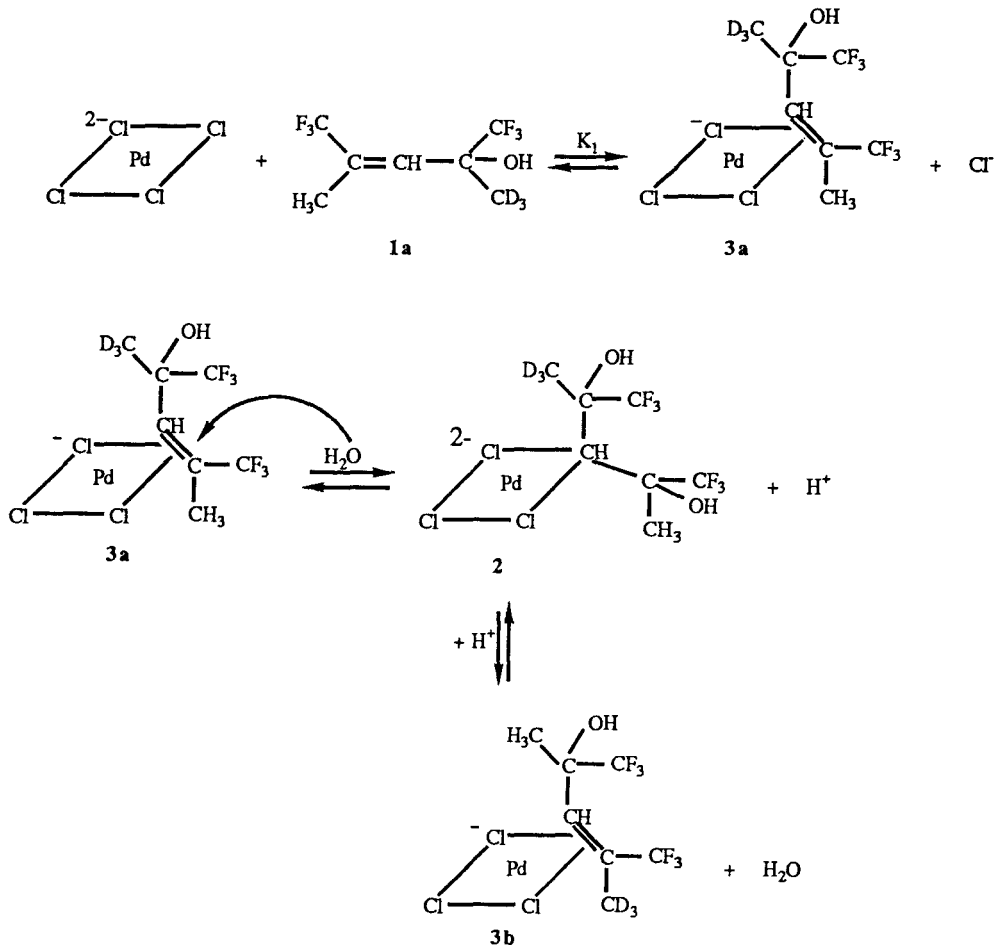
water molecule within the coordination sphere of the catalyst, forming 2, followed by a slow hydroxypalladation step resulting in 4. In this reaction hydroxypalladation is determined as the slow step, see chapter I. This is the only way to explain the appearance of an acid inhibition term in the rate expression. Support is given here to the proposed mechanism for the Wacker oxidation process by Henry[89] in which he states that immediately preceding the hydroxypalladation step, which is the slow step there is an equilibrium loss of a proton from the coordinated water molecule. If Bäckvall's mechanism[101] was operative here then the rate expression would be similar to that of equation III.4 in which there would be no acid inhibition term. A proton

$$\text{Rate} = \frac{k_i[PdCl_4^{2-}][C_7H_5D_3F_6O]}{[Cl^-]^2} \qquad \text{(III.4)}$$

inhibition term would not be expected to appear because the loss of a proton would occur during the rate determining step and not before, as is a necessity for it to appear in the rate expression.

At much higher chloride concentrations, $[Cl^-] \geq 2.0$ M, a change in the rate expression is observed. It is changed to one resembling equation III.2, with no acid inhibition and only an inverse first order chloride term. This has been previously observed for the oxidation of some cyclic olefins,[88b,107,108] and is discussed in chapter I.[5] It is obvious from this result, which is similar to the results of studies in methanol, Chapter II, that the presence of high concentrations of chloride ions is changing the mechanism of hydroxypalladation. Scheme III.4 gives a general picture of the most likely mechanism fitting these results. The high concentrations of chloride ions would be expected to inhibit any equilibrium in which a chloride is lost. In the Wacker mechanism K_1 is larger than K_2,[86a] and so the equilibrium defined by K_2 which is the lost of a second chloride is expected to be affected more than the

Scheme III.4



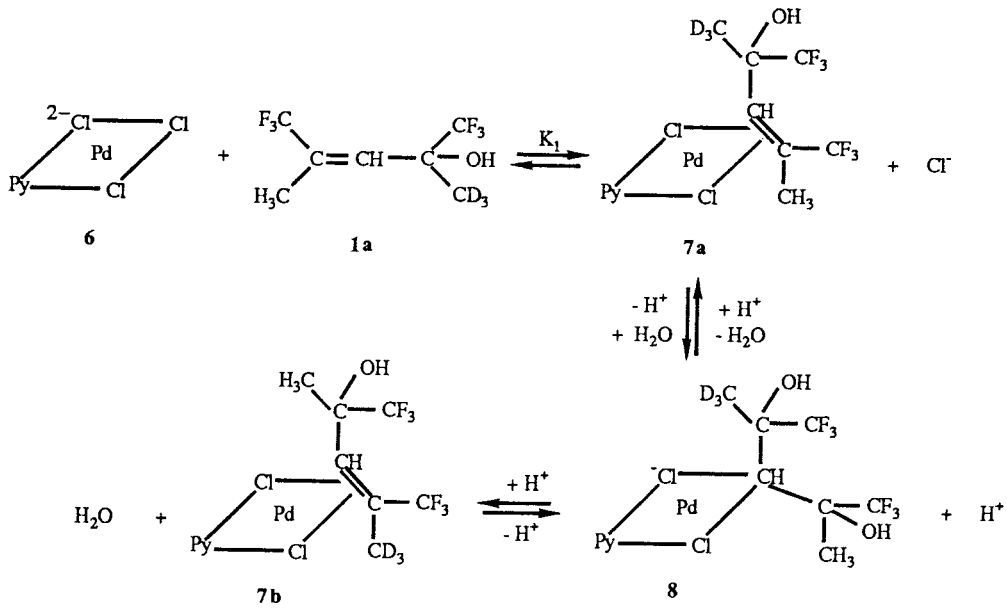
first equilibrium which is the formation of the π-complex, **3a**. The mechanism will hence have a first step, in which the π-complex, **3a**, is formed, thus explaining the chloride inhibition term in the rate expression. The following step would be hydroxy-palladation, resulting from an external attack of a solvent water molecule on the π-bond of the olefin. Since there is no path available for oxidative decomposition then the system can only isomerize and exchange.

How can these results be reconciled with the stereochemical studies of Bäckvall, Åkermark and Ljunggren,[101] who using $CuCl_2$ to trap the intermediate hydroxy-palladation adduct to give 2-chloroethanol, showed that the addition was trans by the

configuration of the product from ethene-1,2-d_2. Their reaction conditions involved high chloride concentrations which greatly retarded the rate of oxidation of ethylene. It was later shown that under these conditions the main process was a non-oxidative exchange and isomerization reaction whose rate expression is similar to equation III.2.[86a] The rate expression is consistent only with a trans attack of water in a manner similar to that shown in equation I.22, but with a chloride replacing the aquo ligand. The extra chloride apparently stabilizes the palladium-σ-hydroxy complex against oxidative decomposition to carbonyl products, in the absence of $CuCl_2$, but apparently $CuCl_2$ can intercept the intermediate causing it to decompose to 2-chloroethanol. This is also clearly demonstrated in studies done in methanol and described in Chapter II.

In order to further test the validity of these results a coordinated chloride of the catalyst, $PdCl_4^{2-}$, was replaced by a strongly complexing neutral ligand, pyridine, and its effect on the nature and rate of isomerization studied kinetically. Table III.3 gives the results of these studies. From these data the rate expression obtained is that given in equation III.3, which is similar to the results of the kinetic studies, done under conditions of high chloride concentration with $PdCl_4^{2-}$ catalyst, given in equation III.2. These results imply that the pyridine is having a similar effect on the reaction process as the high concentrations of chloride ions. Scheme III.5 gives some insight as to the possible effects of this strongly complexing neutral ligand. First there is the strong trans directing effect of this ligand which will direct the incoming olefin to the site in a trans position replacing a coordinated chloride to give **7a**. This π-complex is neutrally charged thus making the other two chlorides inert to replacement as it would result in a positively charged species, in an acid medium. **7a** would be more susceptible to an external attack, not having a negative charge. Both factors would be discouraging of any internal attack of coordinated

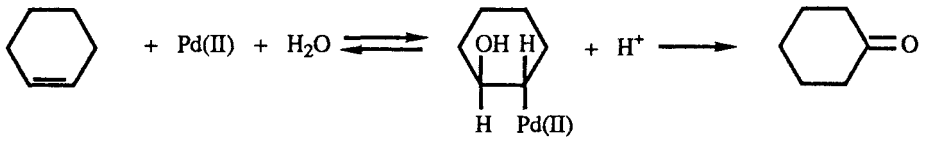
Scheme III.5



water. The exchange kinetics as predicted from these studies gave a rate expression with a single chloride inhibition term and no acid inhibition term. No squared chloride inhibition term was obtained as this would require that both the olefin and a water molecule enter the coordination sphere of the intermediate species.

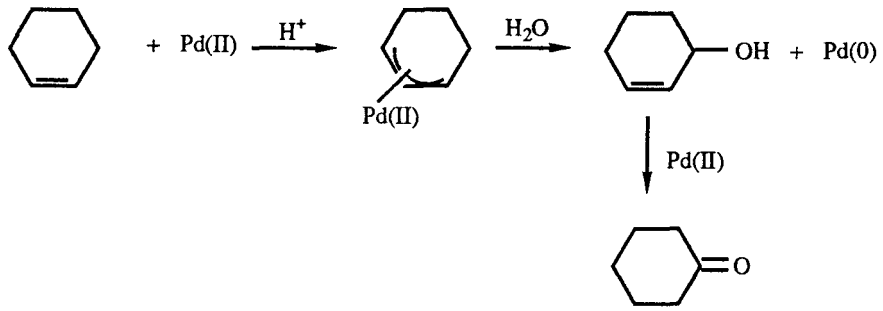
These kinetic results simply indicate that different modes of hydroxypalladation are taking place under different conditions. Thus if two different types of oxypalladation can occur in water it is expected that changing the solvent may also have a profound effect on the mode of oxypalladation. An example is the case of using CO to trap the hydroxypalladation of *cis*-, and trans-2-butene[115] at -25 °C, in a mixture of water/acetonitrile, which resulted in a trans stereochemistry. Both cis and trans addition have been observed in non-aqueous solvents. Some examples of this includes the former mentioned, along with the oxidation of cyclic olefins such as cyclooctadiene are well known trans processes. On the other hand the peroxypalladation of olefins is known to be cis.[160] Even the identity of the olefin

can be important under the Wacker oxidation conditions, as evidenced by the oxidation of cyclohexene,[88b,154] which gives a rate expression with no acid inhibition term. Two possible routes have been proposed, the first of which is shown in equation III.5, and involves *trans* hydroxypalladation due to steric factors, and the



(III.5)

second involving a π-allyl intermediate, equation III.6.



(III.6)

The important point is that general statements to the effect that, "oxygen nucleophiles attack olefins in a trans fashion",[161] are meaningless because the mode of addition could depend on the olefin and the reaction conditions.

D. Experiment

Starting Materials. The palladous chloride was purchased from AESAR. 1,1,1-Trifluoroacetone, sodium (pellets in xylene), phosphorus pentoxide and methyl-d_3-magnesium iodide (Aldrich, Sure-seal) were purchased from Aldrich Chemicals and used without further purification. ^{18}O-water (1.5 atom % and 97 atom %) were obtained from MSD Isotopes inc. All other chemicals were of reagent grade.

Determination of Palladium Concentration in $PdCl_4^{2-}$ and $PdCl_3Py^-$ Stock Solutions with Dimethylglyoxime. Each stock solution of catalyst was standardized by gravimetrically determining the palladium content with dimethylglyoxime. A detailed description of this technique is given in the experimental section of Chapter II.[150]

Isomerization Kinetics. The isomerization of 2-methyl-d_3-4-methyl-1,1,1,4,4,4-hexafluoro-3-penten-2-ol was monitored by using ^2H NMR, a sample spectrum of which can be seen in appendix B.11. The reaction was run on a 10 mL scale. Four experimental points were taken for each run. The first three 2-mL aliquots of the mixture were extracted with 3-5 mL portions of methylene chloride. For the final sample the remainder of the reaction mixture was used. After the mixture was dried with anhydrous $MgSO_4$, filtered and the methylene chloride evaporated at room temperature, the crude concentrate was dissolved in $CHCl_3$ and the solution analyzed by ^2H NMR, using a Varian 300VXR NMR. The % isomerization was determined by comparing the area of the singlet peak at 1.6 ppm corresponding to CD_3 in 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol with the area of the singlet peak at 2.2 ppm corresponding to CD_3 in 2-methyl-4-methyl-d_3-1,1,1,5,5,5-hexafluoro-3-penten-2-ol. $CDCl_3$ (7.24 ppm) was used as internal standard. The data was plotted as a reaction approaching equilibrium.[16] A plot of ln(50% - % isomerization) vs time was made on semilog paper and the half-life read off at the 25% point. Since the

value of the equilibrium constant for the isomerization is equal to 1, the rates of the forward and the reverse reactions are identical and the value of the slope of ln(50% - % isomerization) = $-2k_{obsd}$. The value of k_i at low chloride concentrations ($[Cl^-] \leq 1.0$ M), was calculated by using the expression $k_{obsd} = k_i[PdCl_4^{2-}]/[Cl^-]^2[H^+]$. At high chloride concentrations ($3.0 \text{ M} \geq [Cl^-] \geq 2.0$ M), k_i was determined from the following expression $k_{obsd} = k_i[PdCl_4^{2-}]/[Cl^-]$. Correlation coefficients were better than 0.95.

^{18}O Exchange Kinetics. The experimental procedures were similar to those for the isomerization studies. ^{18}O-isotopic effect on the ^{13}C NMR is a useful tool in studying the exchange kinetics of this system. A ^{13}C NMR spectrum illustrating this induced shift can be seen in appendix B.12. The approach used was similar to that reported by J. M. Risley and R. L. V. Etten.[158] An upfield ^{18}O-isotopic shift of the alcohol carbon which was dependent on the amount of ^{18}O in the molecule. After suitable amounts of the $HClO_4$, Li_2PdCl_4, and LiCl stock solutions were mixed, the solution was diluted with a mixture of 1.5 atom % and 97 atom % water-^{18}O. ^{13}C NMR were run on the Varian VXR 300 MHz NMR. Approximately 3000 transients gave the required sensitivity. The % ^{18}O in the alcohol mixture (2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol and 2-methyl-4-methyl-d_3-2-hydroxy-^{18}O-1,1,1,5,5,5-hexafluoro-3-pentene), were determined by a comparison of the intensities of the ^{13}C parent peak at 74 ppm with the intensities of the product peak at the same resonance, but shifted upfield by 0.08 ppm. Control experiments in the absence of Pd(II) indicated that there was no observable acid catalyzed exchange. The data were plotted as a reaction approaching equilibrium.[157] A plot of $\log(\%^{18}O_\infty - \%$ exchanged) vs time was made on semilog paper and the half-life read off at the 50% point. $\%^{18}O_\infty$ was determined by running the final portion of each experiment for 24 hours and the % isotopic exchange determined as $\%^{18}O_\infty$. The value of k_{obsd} was

determined in a similar way as for that of isomerization. The value of k_{ex} was then calculated from k_{obsd} by using the equation $k_{ex} = k_{obsd}[Cl^-]^2[H^+]/[PdCl_4^{2-}]$.

Preparation of 4-Methyl-1,1,1,5,5,5-hexafluoro-4-pentanol-2-one.[159] One gram atom of sodium pellets, (23.0 g), was prepared in xylene and the xylene removed by means of a sintered-glass filterstick. The sodium pellets were washed twice with ethyl ether and covered with 200 mL of anhydrous ethyl ether. With vigorous stirring 60 g (1.3 moles) of absolute ethanol was added to the sodium over 30 mins. To this well stirred ether solution of sodium ethoxide was added 100 g. (0.89 moles) of 1,1,1-trifluoroacetone, the temperature of the reaction mixture being kept below 0°C. After the solution had been stirred for 1-2 hours, it was poured into a mixture of 100 mL of concentrated sulfuric acid and 1000 g of ice. The solid hydrate was filtered and the aqueous layer neutralized with sodium hydroxide solution and extracted with ethyl ether solvent. Both the residue and the ether extract were combined and distilled giving 69% yield of crude condensation product, b.p. 78-98°C. This crude product was distilled over P_2O_5 giving an overall yield of 65%. b.p. 82°C. 300 MHz ^1H NMR ($CDCl_3$): δ = 1.52 (s, 3H), 2.85 - 3.34 (q, 2H, $^2J_{FH}$ = 14 Hz). ^{13}C ($CDCl_3$): 20, 40, 73, 78, 115, 125, 189. IR (neat): 3500, 1770, 1200.

Preparation of 4-Methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one. To 20 g of 4-hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone was added dropwise 10 mL of 20% oleum over 15 minutes. The mixture was refluxed for 6 hours and distilled giving 18 g (91%) of product boiling at 76°C. 300 MHz ^1H NMR ($CDCl_3$): δ = 2.41 (s, 3H), 6.95 (s, 1H). ^{13}C ($CDCl_3$): 12, 115, 118, 122, 150, 180. IR (neat) 3100, 1740, 1650, 1190.

Preparation of 2-Methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol. To 15 mL of 1.0 M (0.015 moles) of methyl-d_3-magnesiumiodide in anhydrous ethyl ether, was added 1.82 g (0.0081 moles) of 4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one

under a flow of nitrogen. The solution was stirred for 30 minutes and hydrolyzed with 100 mL. of 5% hydrochloric acid. The aqueous layer was separated and neutralized with a saturated solution of sodium carbonate and extracted with 2-50 mL portions of ethyl ether. The ether layers were combined and washed with a saturated solution of sodium sulfite, dried (anhydrous magnesium sulfate) and distilled giving 69% yield of 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol. b.p. 76°C. 300 MHz ^1H NMR ($CDCl_3$): δ = 2.12 (s, 3H), 3.40 (s, OH), 6.18 (s, 1H). ^2H ($CHCl_3$): 1.49 (s, 3D). ^{13}C ($CDCl_3$): 12, 22, 74, 124, 126, 129, 133. IR (neat): 3450, 3020, 2900, 2250, 1150. *Anal.*Calcd for $C_7H_5C_3F_6O$: C, 37.34; H + D (as H), 3.58. Found: C, 36.87; H + D (as H), 3.56.

Preparation of Patassium Trichloropyridine Palladate(II), $KPdCl_3Py$.[162] 9.25 g, (0.0283 mole) of K_2PdCl_4 and 2.39 g, (0.283 mole) of pyridine were suspended in 100 mL of DMF and stirred at room temperature for 4 hours. During this time complete dissolution of the starting materials was achieved, while insoluble KCl appeared. The solution was then kept in the refrigerator for approximately 2 hours to complete the deposition of KCl. It was then filtered and the complexes filtered and the complex precipitated with an isopropyl alcohol/ether mixture, (1:2, 300 mL).

The precipitate was then filtered off and washed with small portions of acetone and ether. The product was then dried in a dessicator at room temperature in the presence of $CaCl_2$ followed by P_2O_5 at 110 °C under vacuum. The yield obtained was 8.09 g, 86.3 %. Melting Point = 300 °C (decomposed).

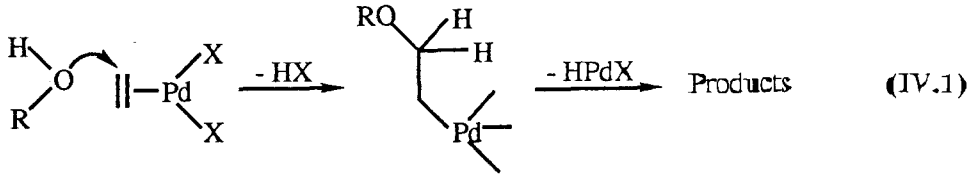
CHAPTER IV

PALLADIUM(II)-CATALYZED OXIDATION AND ISOMERIZATION REACTIONS - EFFECT OF REACTION CONDITIONS ON THE STEREOCHEMISTRY OF THE WACKER REACTION

A. Purpose

Determining the stereochemistry of the hydroxypalladation step in the Wacker oxidation of olefins has been a challenge.

In the oxidative functionalization of olefins by palladium(II) complexes, oxygen nucleophiles, coordinated or uncoordinated to the metal attack the olefin to give an oxypalladation intermediate equation IV.1.[163] Subsequent β-elimination of palladium-



(IV.1)

hydride species leads to products such as acetaldehyde, and the resulting HPdX species decomposes to give palladium(0) and HX. This process for the Wacker oxidation of olefins has been extensively discussed in Chapter I.

As previously mentioned, there has been considerable difficulty in determining the stereochemistry of the oxypalladation process from the final products of oxidation without altering the reaction conditions to give products that will permit

stereochemical results. Hence it has been previously reported that the hydroxypalladation process results from a distal addition of H_2O, (trans hydroxypalladation),[101] while mechanistic results have led to conclusions to the contrary, a syn addition of a coordinated ^-OH group, (cis hydroxypalladation).[86a]

In this project a chiral allylic alcohol will be oxidized under Wacker oxidation conditions. This allylic alcohol should allow the hydroxypalladation step of the Wacker oxidation which is stereospecific for the mechanism proposed by Henry[86a], or Bäckvall,[101] to be determined, if either of these mechanisms is active. This will result in a 1,3-chirality transfer of optically active centers, thus allowing analysis of the stereochemistry of the product and will give insight into the actual mode of hydroxypalladation of the Wacker reaction.

The modes of oxypalladation for isomerization will be investigated using a chiral tetrasubstituted allylic alcohol which cannot be oxidized but only isomerized as described for the substrate studied in Chapter III.

The effect of various variables on the mode of the hydroxypalladation step will be investigated using this probe, namely: (1) varying chloride concentrations; (2) the presence of a strongly complexing neutral ligand, and (3) variation of the substrate.

The information gathered will be useful in the designing of catalysts suited for various purposes such as exchange and oxidation.

B. Results

Characterization of (E) and (Z)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one. The (E)- and (Z)-isomers of 4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one[159] were synthesized by aldol condensation of 1,1,1-trifluoroacetone, followed by rapid dehydration of the product with 20 % oleum. They were obtained in the ratio 95.5 : 4.5, (E : Z). These conformers were separated by GC on a 20ft. x 0.85 in. DCQF-1 column, at 120 °C, with a helium flow rate of 20 mL/min., after fractional distillation.

The E-isomer had a boiling point of 76°C, and a retention time of 12 minutes. The following data were compiled: ^{1}H NMR, ($CDCL_3$): δ = 2.41 (s, 3H), 6.92 (s, 1H); ^{13}C ($CDCl_3$): 16, 117, 119, 121, 150, 180. IR 3100, 2960, 1735, 1650, 1200, 1100, 735. *Anal.* Calcd for $C_6H_4F_6O$: C, 34.97; H, 1.96. Found: C, 34.91, H, 1.90.

The Z-isomer had a boiling point of 95 °C, and a retention time of 33 minutes. Spectroscopic data for the Z-isomer are as follows; ^{1}H NMR ($CDCL_3$): δ = 1.74 (s, 3H), 6.00 (s, 1H); ^{13}C ($CHCl_3$): 20, 80, 96, 119.5, 120, 122, 124, 128, 144. IR: 3110, 3000, 2960, 1750, 1690, 1635, 1180, 735. *Anal.* Calcd for $C_6H_4F_6O$: C, 34.97; H, 1.96. Found: C, 35.05; H, 1.63. Due to steric factors the Z-isomer was expected to be the major isomer as similar results were obtained for crotyl chloride and crotyl alcohol by Lum et al,[164] and illustrated by Bumgardner and workers.[165]

The Z-isomer was not used for further work as it was the minor product. Two rotamers were observed for each isomer.[116] The barriers of separation of the rotamers for the E-isomer was only 16.6 kcal, which at 25°C is easily overridden, see Figure IV.1. However the barrier of rotation for the Z-isomer was 32.2 kcal which is surmountable only at higher temperatures, thus allowing the both rotamers to be stable at room temperature, see Figure IV.2. This is observed in the complicated NMR spectra obtained for the Z-conformer. Table IV.1 illustrates the spectral

Table IV.1. Comparison of major spectral differences between (E)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one, and (Z)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one.

	(E)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one	(Z)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one
IR	1735 cm^{-1} (C=O)	1680(2), 1750 cm^{-1}(1) (C=O)
	1650 (C=C)	1635 (C=C)
NMR (^1H)	6.90 ppm (s, 1H)-vinyl	6.0 ppm (s, 1H)-vinyl
	2.35 (s, 3H)-methyl	1.7 (s, 3H)-methyl
(^1H NOESY)	+1.6 %	+36 %
(^{13}C)	180 (C=O)	144 (C=O)
	17 ($\underline{CH_3}$-C=)	20 ($\underline{CH_3}$-C=)
	150 (SP^2 Carbon)	

differences between both conformers.

(E)-4-methyl-3-penten-2-one was enantioselectively reduced with lithium

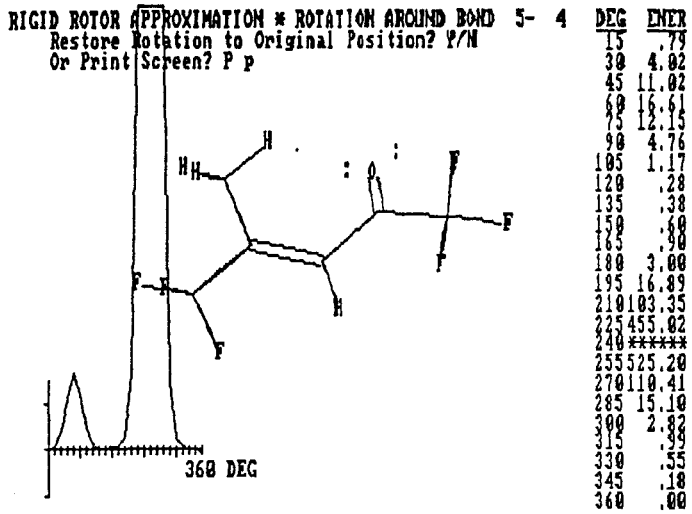


Figure IV.1 MMX diagram of E-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one, showing rotation about C2 and C3. Energies are in Kcal/mole.

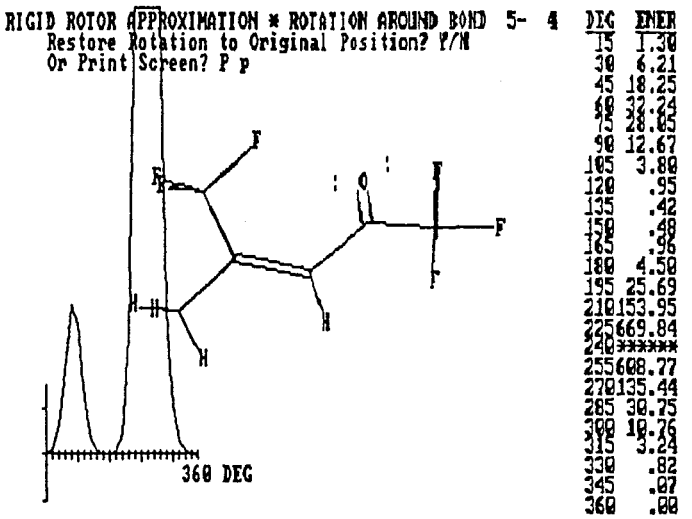


Figure IV.2. MMX diagram of Z-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one, showing rotation about C2 and C3. Energies are in Kcal/mole.

aluminum hydride, modified by 1 equivalent of (L)-N-methyl ephredrine[166] and 2

equivalents of 3,5-xylenol. 4-Methyl-3-penten-2-ol was obtained in 83.8% yield, bp 118 - 122°C, $[\alpha^{22}_D]$ = 02.06° ± 0.02. Preparation of the MTPA ester[167] and NMR studies revealed a 18% ee favoring the R-enantiomer. From this $[\alpha^{22}_D]_{max}$ =-11.4° ± 0.1° was determined for the alcohol. The diastereomers were collected separately from a 20 ft x 0.21 in. DCQF-1 column, at 190 °C, helium flow rate 60 mL/min. Retention times were 174 for the RS- and 180 min. for the RR-diastereomers. The first diastereomer collected showed a 50% ee by NMR and the alcohol after hydrolysis gave $[\alpha^{22}_D]$ = 5.81° ± 0.01°(c,2.0,$CHCL_3$) which corrects to a $[\alpha^{22}_D]_{max}$ = 11.6° ± 0.01°.

Lanthanide induced shift studies were done on this sample, using $Eu(fod)_3$. NMR was use to study the induced shift (LIS) of the methoxy proton resonance. $Eu(fod)_3$ shift analysis revealed that this corresponded to the (S)-(-)- enantiomer (RS-diastereomer). In this case the OCH_3 signal of the (R,R) diastereomer appeared at higher field than the (R,S) diastereomer in the absence of $Eu(FOD)_3$, Figure IV.3.

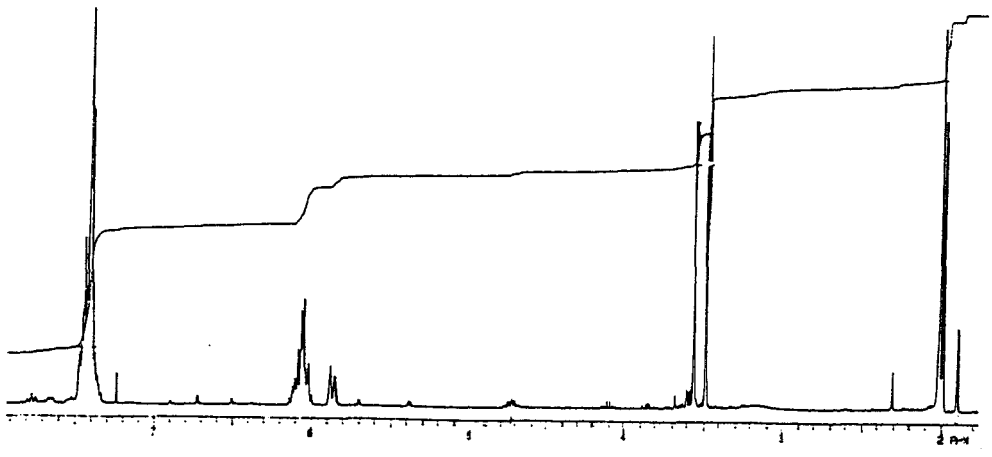


Figure IV.3. ^1H NMR of a mixture of RR and RS diastereomers of 4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-yl-α-methoxy-α-(trifluoromethyl) phenylacetate.

The OCH_3 signal of the (R,R) diastereomer shifts further downfield passing over the signal of (R,S) diastereomer by the progressive addition of $Eu(fod)_3$. This is illustrated in the LIS plot shown in figure IV.4.

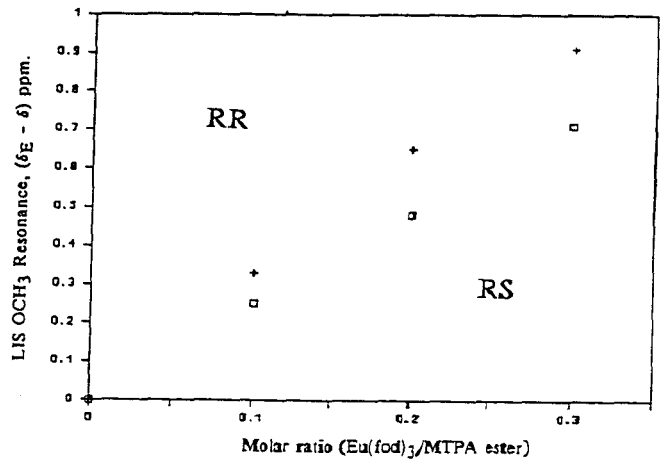


Figure IV.4. Representative plots of lanthanide induced shift (LIS), of the methoxy proton resonance vs. molar ratios of $Eu(fod)_3$ for the diastereomeric esters of 4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol. δ_E is the chemical shift in ppm for the OCH_3 signal in the presence of a specified molar ratio of $Eu(fod)_3$ in $CDCl_3$ solvent, while δ is the normal chemical shift. The difference in the slope of these two lines is designated *ΔLIS value.*

Reduction of the RR-diastereomer (100% pure, collected from GC), using $LiAlH_4$ in ether confirmed that $[\alpha^{22}D]_{max}$ = -11.4° ± 0.1° for (-)-(R)-(E)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol.

(+)-(S)-(E) and (-)-(R)-(E)-2-Methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol were charactized by a similar technique, giving the following results were obtained. The RR and RS-MTPA derivative of this alcohol were similarly separated by GC at 185 °C, and helium flow rate of 60 mL/min. Retention times were 114 min. for the RS and 138 min. for the RR diastereo isomers. Lanthanide induced shift

studies with $Eu(fod)_3$ and subsequent hydrolysis with $LiAlH_4$ revealed the (+)-(S)-(E) enantiomer gave $[\alpha^{22}D]_{max}$ = +9.5° ± 0.1°(c, 2.0, $CHCl_3$), and the (-)-(R)-(E) enantiomer, $[\alpha^{22}D]_{max}$ = -9.3° ± 0.3°.

Oxidation and isomerization Products. Oxidation of the racemic alcohol in water under Wacker oxidation conditions with $PdCl_4^{2-}$ as catalyst has yielded only the desired oxidation product, 4-hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone isolated as the 2,4-DNP derivative.

The kinetic results given in Table IV.2 indicated that the oxidation of 4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol in water under conditions similar to those reported for the oxidation of ethene in water, has a rate expression similar to the Wacker rate expression, equation IV.2, with average k_{ox} = 1.7 x 10^{-6} M^2s^{-1}. The

$$\text{Rate} = \frac{k_{obs}[PdCl_4^{2-}][C_6H_6F_6O]}{[Cl^-]^2[H^+]} \qquad \text{(IV.2)}$$

dependence of the rate on chloride concentrations was derived from linear plots of k_{obs} vs squared chloride concentrations for runs 1, 4, 5, 9 and 10. A squared chloride inhibition dependence was found. A first order acid inhibition term was obtained after similar plots were made for $1/[H^+]$ vs k_{obs} for runs 1, 6 and 7. Linear plots of k_{obs} vs [Pd(II)] which were done for runs 1 to 3 and 8, gave a first order dependence of the rate on palladium(II) concentration. From these results it was obvious that equation IV.2 was valid, since average k_{ox} = 1.7 x 10^{-6} M^2s^{-1} remained constant for runs 1 to 10.[157]

The MTPA ester derivative of this product was made in yields of 90 % and the GC retention times of the respective diastereomers corresponded to that of the authentic samples.

In the presence of $PdCl_3Py^-$ catalyst oxidation was observed for 4-methyl-

Table IV.2. Rates of oxidation of 4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol in aqueous solution[a] with varying concentrations of acid,[b] chloride,[c] and palladous ions.

run	$[H^+]$	$[Cl^-]$	$10^2[PdCl_4^{2-}]$	$10^6 k_{obs}$, s^{-1}	$10^6 k_{ox}$,[d] $M^2\ s^{-1}$
1	0.10	0.40	2.0	2.2	1.8
2	0.10	0.40	4.0	4.0	1.6
3	0.10	0.40	8.0	8.2	1.6
4	0.10	0.20	2.0	7.0	1.4
5	0.10	0.80	2.0	0.53	1.7
6	0.20	0.40	2.0	1.3	2.1
7	0.40	0.20	2.0	2.1	1.7
8	0.40	0.20	16.0	15.9	1.6
9	0.10	0.10	2.0	31.2	1.6
10	0.10	0.05	2.0	124	1.4
				Average	1.7

[a]Reactions were carried out at 25 °C in a constant temperature water bath, using the potentiometric technique, described in the experimental. μ was kept at 2.0 M with addition of the appropriate amounts of $LiClO_4$. [b]Added as $HClO_4$. [c]Added as LiCl.. [d]Determined by the equation $k_{obs} = k_{ox}[PdCl_4^{2-}]/[Cl^-]^2[H^+]$, assuming that equation IV.1 was correct and the concentrations of chloride, acid, and palladous ions were constant.

Table IV.3. Product distribution of the oxidation and isomerization of ethylene with $PdCl_3Py^-$ in the presence of $CuCl_2$.[a]

$[CuCl_2]$	% Acetaldehyde	% 2-Chloroethanol
0.0	100.0	0.0
1.0	100.0	0.0
4.0	52.8	47.2
5.0	32.0	68.0
6.0	17.0	83.0
8.0	2.0	98.0

[a]Conditions: $[Cl^-]$ = 0.2 M, $[H^+]$ = 0.4 M, [Pd(II)] = 0.082 M, T = 25 °C. All runs were carried out under 1 atm of ethylene pressure. [b]Determined by ^1H NMR.

1,1,1,5,5,5-hexafluoro-3-penten-2-ol only at low chloride and acid concentrations, (0.05 M). With ethylene as substrate, oxidation was obtained under conditions of chloride ion concentrations less than 0.2 M, in the presence of quinone as reoxidant, or in the absence of any reoxidant. When $CuCl_2$ was used for reoxidizing the reduced palladium species at the low chloride concentrations, a mixture of acetaldehyde and 2-chloroethanol were obtained, as is shown in Table IV.3. At $CuCl_2$ concentrations < 2.0 M, acetaldehyde was the only product detected. Its formation is due to the an oxidation process similar to the Wacker oxidation. At concentrations greater than or equal to 4.0 M a mixture of acetaldehyde and 2-chloroethanol were the dominant products with traces of ethanol present. As the concentration of $CuCl_2$ was progressively increased 2-chloroethanol became the dominant product. The isomerization and exchange studies of 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol are reported and discussed in Chapter III.

Kinetic studies. With $PdCl_3Py^-$ as catalyst the kinetics of the oxidation of ethylene was studied. Table IV.4 gives the result of the determination of K_1 according to the equilibrium in equation IV.3. An average of 20.3 was obtained for

$$PdCl_3Py^- + C_2H_4 \underset{}{\overset{K_1}{\rightleftharpoons}} PdCl_2Py(C_2H_4) + Cl^- \qquad (IV.3)$$

K_1 which is close to the value determined for the similar equilibrium with $PdCl_4^{2-}$ as catalyst.[86a] Table IV.5 gives the results for the kinetics of the rate of oxidation. A single acid inhibition dependence of the rate was determined when k_{obs} was plotted against $1/[H^+]$ for runs 19, 23, 24 and 26. For similar plots of k_{obs} vs inverse chloride concentrations for runs 18 to 20 and 25, a squared chloride inhibition was obtained. When $[PdCl_3Py^-]$ was treated similarly for runs 19, 21 and 22 the rate was found to have a first order dependence on the catalyst. These

Table IV.4. Studies of the initial ethylene uptake in aqueous acid solution at 25 °C by potasium trichloropyridine palladate(II), $KPdCl_3Py$. Determination of K_1.[a]

run	$[Cl^-]$	$10^4[PdCl_2PyC_2H_4]$	$10^3[(PdCl_3Py)^-]$	$[Cl^-]_e$	K_1[b]
11	1.0	4.10	9.59	1.00041	20.4
12	0.8	5.02	9.50	0.800502	20.1
13	0.6	6.58	9.34	0.600658	20.2
14	0.4	11.1	8.89	0.40111	23.9
15	0.2	18.9	8.11	0.20189	22.4
16	0.1	26.0	7.40	0.1076	17.4
17	0.05	41.0	5.91	0.0541	17.9
				Average	20.3

[a]Conditions: $[H^+]$ and [Pd(II)] were kept constant at 0.50 M, and 0.01 M. μ was maintained at 2.0 M with $LiClO_4$. Initial $[C_2H_4]$ was 2.1 x 10^{-3} M. $[Cl^-]_e$ is concentration of free chloride at equilibrium. [b]Average of at least five runs.

Table IV.5. Kinetics for ethylene oxidation catalyzed by potassium trichloropyridine palladate(II), in aqueous acid solution at very low chloride concentrations.[a]

run	$[Cl^-]^b$	$[H^+]^c$	$[PdCl_3Py^-]$	$10^8 k_{obs}$ s^{-1}[d]	$10^9 k_{ox}$, M^2 s^{-1}[e]
18	0.2	0.5	0.01	0.36	7.2
19	0.1	0.5	0.01	1.35	6.8
20	0.05	0.5	0.01	5.1	6.4
21	0.1	0.5	0.02	2.9	7.3
22	0.1	0.5	0.005	0.71	7.1
23	0.1	0.25	0.01	2.75	6.9
24	0.1	1.0	0.01	0.65	6.5
25	0.025	0.5	0.01	22.3	7.0
26	0.05	0.1	0.01	27.0	6.8
				Average	6.9

[a]Conditions: quinone = 0.2 M, μ = 2 by addition of appropriate amounts of $LiClO_4$, T = 25 °C. All runs were done under 1 atm. of ethylene pressure. [b]Added as LiCl. [c]Added as $HClO_4$. [d]Calculated as a first order decrease in ethylene with correlation coefficients greater than 95 %. [e]$k_{ox} = k_{obs}[Cl^-]^2[H^+]/[PdCl_3Py^-]$

resulting are consistent only with equation IV.4, with an average k_{ox} of 6.9 x 10^{-9}

$$\text{Rate} = \frac{k_{obs}[PdCl_3Py^-][C_2H_4]}{[Cl^-]^2[H^+]} \qquad \text{(VI.4)}$$

M^2s^{-1}. The rate of oxidation is much slower than the Wacker oxidation with $PdCl_4^{2-}$ as catalyst.[86a] However the fact that both rate expressions and equation IV.2 are similar implies that similar mechanisms are operative.

The kinetics of the isomerization and exchange of 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol are reported and discussed in Chapter III.

The stereochemistry of oxidation and isomerization. The stereochemistry of the oxidations were done using 99.2 % ee (E)-(R)-(+)- and 100 % ee (E)-(S)-(-)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol as the starting allylic alcohols, in water under the conditions described in Table IV.6. Following the outline in Scheme I.6, page 33, at low chloride concentrations only oxidation was observed. This was monitored by ^1H NMR and GC retention times, (the retention times are for the MTPA diastereomers of the starting alcohols). Starting with (R)-(-)-(E)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol there is no chiral center inversion, but instead a chirality transfer, forming a new chiral center where the incoming hydroxy group attaches, resulting in the formation of (S)-(+)-4-hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone, which is of the opposite configuration from the starting alcohol. When the starting alcohol was the (S)-(+)- enantiomer, the product was the (R)-(-)- form. At chloride ion concentrations greater than or equal to 2.0 M no oxidation occurred. Very little isomerization was detected by ^1H NMR and the starting material was obtained unchanged from the initial enantiomer. The results clearly show an inversion of configuration from the starting alcohol to the β-hydroxy-ketone oxidation product.

Table IV.6. Stereochemistry and distribution of oxidation products from chiral allylic alcohol[a] in aqueous acid solution.[b]

Starting Alcohol			Product		
configuration	% ee[c]	[Cl^-]	configuration	% ee[c] oxidation[d]	% isomerization[e]
(R)-(-)	99.2	0.1	(S)-(+)	100.0	0.0
(R)-(-)	99.2	0.5	(S)-(+)	99.8	0.0
(R)-(-)	99.2	2.0	-------	-----	2.0[f]
(R)-(-)	99.2	3.5	-------	-----	0.45[f]
(R)-(-)[g]	99.2	0.05	(S)-(+)	22.0	17.0
(S)-(+)	100.0	0.3	(R)-(-)	97.0	0.0
(S)-(+)	100.0	1.0	(R)-(-)	94.0	0.0
(S)-(+)	100.0	2.5	-------	-----	1.2[f]
(S)-(+)	100.0	5.0	-------	-----	0.2[f]
(S)-(+)[g]	100.0	0.05	(R)-(-)	12.0	12.0

[a]Starting alcohol was (E)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol, which was separated and characterized using Mosher's acid, MTPA.[167] [b]Acid and palladous concentrations were kept constant at 0.5 M and 0.05 M respectively. [c]Determined by integration of OCH_3 singlets in ^1H NMR of MTPA-ester, and GC peaks of RR- and RS MTPA diastereomers. [d]Oxidation product is 4-hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone. [e]Isomerization product is 2-hydroxy-2-methyl-1,1,1,5,5,5-hexafluoro-3-pentene. [f]No oxidation products were obtained, and very little isomerization was observed by ^1H NMR. [g]Results of oxidations with $PdCl_3Py^-$ catalyst. All other oxidations were carried out in the presence of $PdCl_4^{2-}$.

The isomerization of (-)-(R)-(E)- and (+)-(S)-(E)-2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol, having 100 % ee, by $PdCl_4^{2-}$ and $PdCl_3Py^-$, to 2-methyl-4-methyl-d_3-1,1,1,5,5,5-hexafluoro-3-penten-2-ol were studied by ^1H NMR. The stereochemistry of the mode of hydroxypalladation was investigated by observing the GC retention times of the MTPA diastereomers. These studies were carried out at various chloride concentrations.

The results reported in Table IV.7 indicate that with $PdCl_4^{2-}$ catalyst under conditions of low [Cl^-], ($\leq$ 0.1 M), an inversion of configuration is obtained. The % inversion is equal to the % isomerization. At high chloride concentrations, approximately 2.0 M, retention of configuration is the observed result, and no inversion is found.

With $PdCl_3py^-$ as catalyst an inversion of configuration of both the (R)- and (S)- enantiomers were obtained at chloride concentration equal to 0.05 M. The % inversion was however consistently lower than the % isomerization at this concentration. For the (R)- enantiomer while the % isomerization was 40 %, the % inversion was only 15 %, and for the (S)- enantiomer, the % isomerization was 25 % while the % inversion was 7.5 %. No inversion was observed at chloride concentrations of 0.2 M or greater. An important result, is that at high chloride, the product obtained from the (-)-(R)-(E) enantiomer was the (-)-(R)-(Z) isomer as product. The same result was obtained for the (+)-(S)-(E) starting alcohol, where the (+)-(S)-(Z) isomer was obtained upon isomerization. These results were confirmed by comparisons with the ^1H NMR and GC retention times of the authentic compounds.

Table IV.7. Stereochemistry of the isomerization products from a tetrasubstituted chiral allylic alcohol[a] in aqueous acid solution,[b] catalyzed by palladium(II).

Substrate				Product		
Config	% ee_c	$[Cl^-]$	[Catalyst]	% Isomerization[d]	% S[e]	% R[e]
R	100	0.10	$PdCl_4^{2-}$	30	32.5[f]	67.5
R	100	0.05	$PdCl_4^{2-}$	48	50.0[f]	50.0
S	100	0.10	$PdCl_4^{2-}$	25	72.5	27.5[f]
S	100	0.05	$PdCl_4^{2-}$	50	50.0	50.0[f]
R	100	2.0	$PdCl_4^{2-}$	31(30)[g]	0.0	100
R	100	3.5	$PdCl_4^{2-}$	27(25)[g]	0.0	100
S	100	2.0	$PdCl_4^{2-}$	35(32)[g]	100	0.0
R	100	3.5	$PdCl_4^{2-}$	45(45)[g]	100	0.0
R	100	0.05	$PdCl_3Py^-$	40[h]	15.0	85.0
S	100	0.05	$PdCl_3Py^-$	25[h]	92.5	7.50
R	100	0.20	$PdCl_3Py^-$	28(28)[g]	0.0	100
S	100	0.20	$PdCl_3Py^-$	32(30)[g]	100	0.0

[a]Starting alcohol was (E)-2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol which was separated and characterized using Mosher's acid, MTPA.[167] [b]Acid and palladous concentrations were kept constant at 0.20 M and 0.05 M respectively. [c]Determined by ^1H NMR of the OCH_3 singlet of the MTPA ester, and GC peaks of the RR and RS diastereomers respectively. [d]Maximum % isomerization obtainable is 50 %b as described in Chapter III. This is determined by ^2H NMR of the CD_3 resonance. [e]Determined by GC retention times of the MTPA diastereomers. [f]Obtained as the (E)- geometric isomer. [g]Value given in parenthesis indicate % obtained as the (Z)- geometric isomer. [h]Obtained as a mixture of (E)- and (Z)- geometric isomers.

C. Discussion

For a valid study of the stereochemistry of the oxypalladation step of the Wacker oxidation of olefins, certain conditions must be met. (1) A substrate which upon oxidation to an aldehyde or ketone gives an indication of the stereochemistry of the hydroxypalladation process. (2) This substrate should obey the Wacker oxidation kinetics.[86a] (3) The oxidation process should be carried out under exact conditions of the Wacker oxidation of ethylene. An allylic alcohol which met these requirements is 4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol, Figure IV.5.

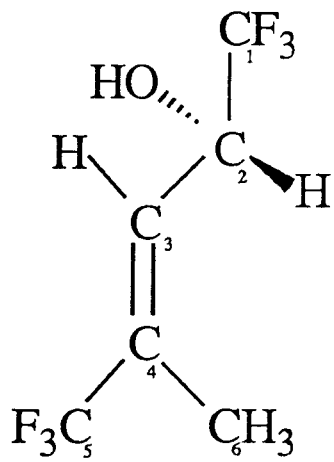


Figure IV.5. (S)-E-4-Methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol.

Synthesis of the starting alcohol yielded a E-(trans) orientation of the substituents about the C=C as the major kinetic product. This orientation is dominant due to the steric blocking of the CF_3 group and the large -$CHCF_3$(OH) moiety. In spite of less steric interaction between the CH_3 group and the large alcoholic neighbor there is still some restriction in this molecule.

Models, and the use of the MMX computer program[116] has shown restricted rotation about the alcohol-vinyl carbon bond, C2-C3, for the R- and S- enantiomers,

Figure IV.6 and IV.7. In both cases this forces the OH and CF_3 groups

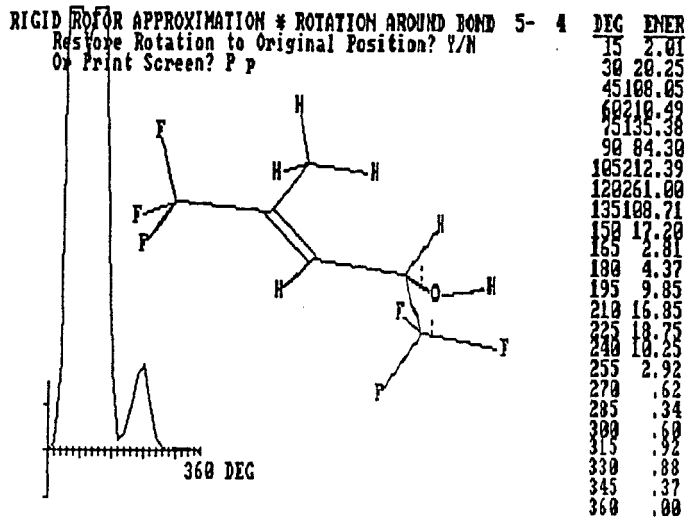


Figure IV.6. MMX diagram of (R)-E-4-methyl-**1**,1,1,5,5,5-hexafluuoro-3-penten-2-ol, showing restricted rotation about C2 and C3. Energies are in Kcal/mole.

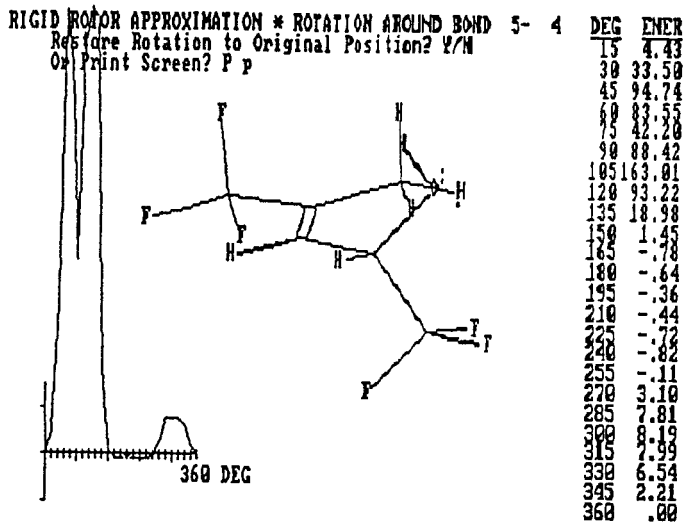


Figure IV.7. MMX diagram of (S)-E-4-methyl-1,**1**,1,5,5,5-hexafluoro-3-penten-2-ol, showing restricted rotation about C2 and C3. Energies are in Kcal/mole.

to a position with greatest distance from the CH_3 group.

The results reflect an inversion of configuration in the process of the 1,3-

transfer of the chiral center. Figure IV.8 gives the outline of this process. The

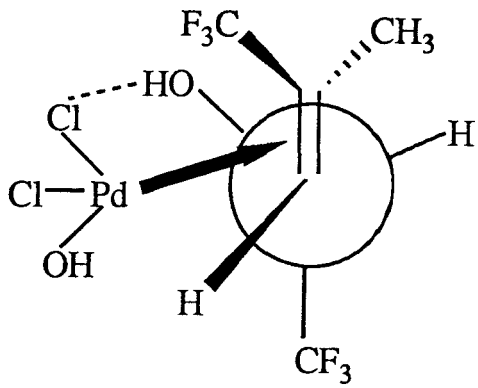
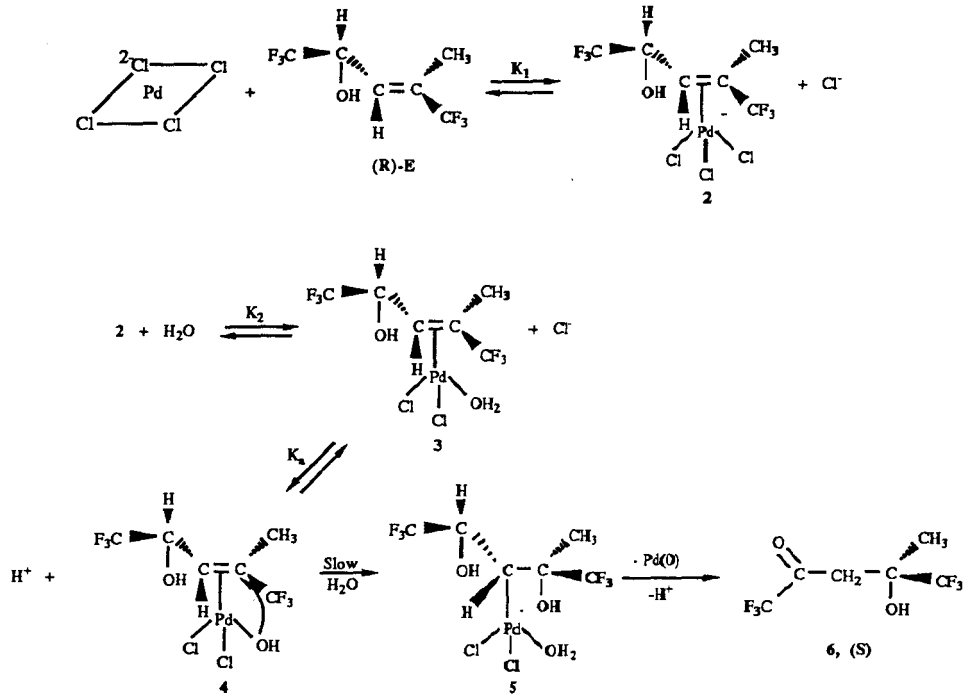


Figure IV.8. 1,3 Chirality transfer and conformational analysis.

diastereofacial selection observed is qualitatively predictable by Cram's rule[117] and can be rationalized by assuming the least sterically hindered models using a perpendicular rotamer as being operative during the reaction. A similar model has being proposed for some catalyzed epoxidation reactions, in which a strong directing effect of a hydroxyl group predominates over those of bulky substituents.[118-122] Thus palladium(II) is predicted to have added to the same side of the double bond as the OH group. This OH group is lying on the least hindered face of the molecule. To comply with the results hydroxypalladation must occur from the side syn to the palladium(II) group leading to the σ-complex. The ensuing intermediate can now freely rotate about all bonds thus allowing the hydrogen on C2 in a β-position to the palladium to arrange itself cis for a hydride abstraction leading to a successful oxidation of C-1 to a ketone group. The most likely mechanism fitting these results, is one as described in Scheme IV.1, resembling that proposed for the Wacker oxidation of ethylene by Henry.[86a] Starting with the chiral allylic alcohol (R)-1 the first step involves the formation of the palladium(II)-π-complex, 2, accompanied with

Scheme IV.1



the loss of a coordinated chloride. It has been shown that the tetrachloro palladate(II) coordinates to the π-bond in a position syn to the OH group. There are suggestions that this strong directing influence of the OH group could be due to hydrogen bonding, and that it dominates over steric factors.[5] With restricted rotation of this group the incoming catalyst will also be restricted to one side. The metal-π-complex, **2**, will then undergo substitution of a second coordinated chloride by a water molecule forming **3**. The OH_2 ligand on **3** is very labile and in effect acts as a vacant site on the catalyst. An equilibrium defined by K_a in which a H^+ is lost from the coordinated H_2O results in the formation of **4**, where a less labile OH replaces the water ligand. From the stereochemical results and following Scheme I.6, the next step, hydroxypalladation, can only occur via attack of an OH from a position syn to the palladium(II) moiety giving **5**. This can only be the attack of a coordinated OH group. The σ-bonded intermediate, **5**, which results, has the new hydroxyl group attaching to C4 resulting in a tertiary alcoholic center. The

palladium(II) will migrate to C3 which is the least sterically crowded region of the molecule. With the formation of the palladium-σ-bonded intermediate, **5**, the molecule is less restricted and has less torsional strain allowing for free rotation about all bonds. The tertiary alcohol center, C4, cannot be oxidized for absence of a H available for transfer to the site of the metal in this step.[89] On the other hand C-2 which is the original secondary alcohol center can be easily oxidized giving the obtained product, **6**, with high optical purity. From this result it is obvious that the mechanism proposed by Bäckvall[101] involving an equilibrium hydroxypalladation followed by a slow step is invalid for this substrate, 4-methyl,1,1,1,5,5,5-hexafluoro-3-penten-2-ol, as the stereochemical results would be expected to be the opposite of that obtained. Since this reaction has the similar kinetic results as that of the Wacker reaction for the oxidation of ethylene under the oxidation conditions studied, it can be assumed that their chemistry of oxidation under these conditions are similar, thus we have solved the Wacker controversy which has been going on for over 25 years.

The effect of a monodentate ligand containing nitrogen as the coordinating atom, on the mechanism of the Wacker reaction, has been also investigated. This ligand is pyridine with the remaining ligands on the palladium(II) center being chlorides.

As summarized in Table IV.2, when ethylene was used as substrate for this new catalyst, $PdCl_3Py^-$, a different distribution of products were obtained which was dependent on the concentration of cupric chloride in solution. At very low cupric chloride concentration of 0.2 M, and up to 1.0 M $CuCl_2$ only oxidation to acetaldehyde was observed. As the concentration of $CuCl_2$ was increased to 8.0 M the % of acetaldehyde steadily decreased while a second product, 2-chloroethanol increased steadily. At $[CuCl_2]$ = 8.0 M, 98 % of the product obtained was 2-

chloroethanol. It can be determined from these results that two mechanisms leading to acetaldehyde and 2-chloroethanol was in operation, and depended on the concentrations of cupric chloride in solution. This is represented in equation IV.5.

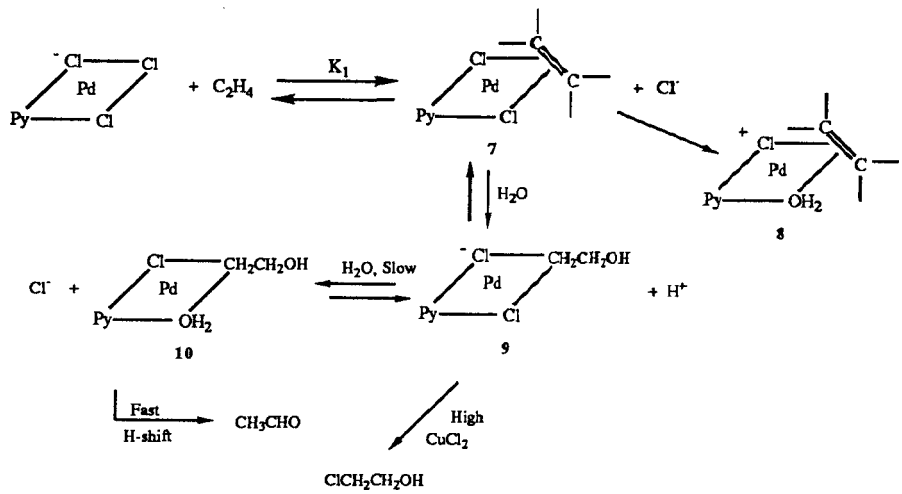
$$C_2H_4 + PdCl_3Py^- \xrightarrow{\text{High } CuCl_2,Cl^-} ClCH_2CH_2OH \qquad \text{(IV.5)}$$
$$\xrightarrow[\text{Low } CuCl_2,Cl^-]{} CH_3CHO$$

The kinetics of the oxidation process at low chloride concentrations were investigated by "gas uptake techniques", described in the experimental. A $K_1 = 20.3$ was obtained. This was equal to that of K_1 determined for the Wacker oxidation of ethylene with $PdCl_4^{2-}$ as catalyst. The rate expression obtained under conditions of low chloride concentrations is given in equation IV.6. The expression closely

$$\text{Rate} = \frac{k[PdCl_3Py^-][C_2H_4]}{[Cl^-]^2[H^+]} \qquad \text{(IV.6)}$$

resembles that of the analogous reaction of ethylene with $PdCl_4^{2-}$ as the catalyst. However k_{ox} was of the order of 10^{-9} M^2s^{-1} which was very low compared to the corresponding process in the Wacker kinetics. The mechanism outlined in Scheme IV.2 gives the best explanation for these results. First the initial rapid uptake of ethylene forming the palladium(II)-π-complex, 7, is fast. The small value of k_{ox} obtained however is an indication that this complex is stabilized by the presence of the less labile pyridine ligand. It can be infered that the readiness at which a second chloride is lost from the coordination sphere of the catalyst to form **8**, is highly reduced. Hence it is likely that trans hydroxypalladation follows to form **9**. With a negative charge on the complex, it becomes easier to loose a second chloride from within the coordination sphere of the palladium(II) center to give **10**, thus creating the vacant site necessary for the oxidative decomposition to proceed.

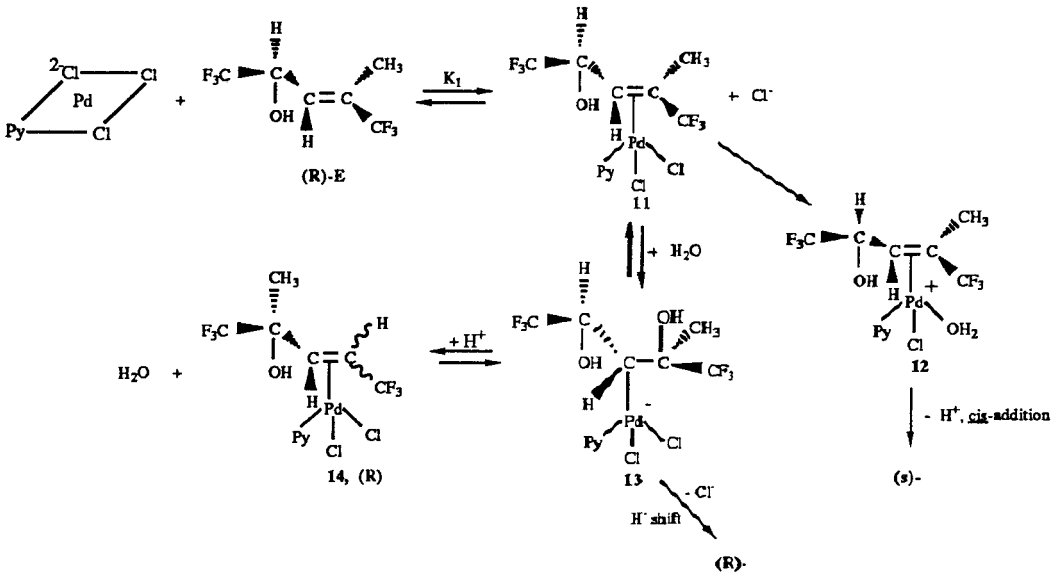
Scheme IV.2



Oxidation by hydride shift consequently gives acetaldehyde. The need for a vacant site to be available, thus facilitating hydride shift, leading to oxidative decomposition has been shown by Henry in previous work done on the Wacker oxidation process, and Whitesides in previous work done with platinum hydrides.[89,128] At $[Cl^-] \geq 0.4$ M, in the presence of cupric chloride, oxidation becomes less important and the hydroxypalladation intermediate is trapped giving the dominant product as 2-chloroethanol. At intermediate concentrations of cupric chloride a mixture of both products was obtained.

Using $PdCl_3Py^-$, the oxidation of 4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol at 0.05 M chloride is accompanied by a reduction in % ee. The maximum % ee obtained was 17 % for the (R)-(-) enantiomer starting alcohol as substrate. At higher chloride concentrations only isomerization was detected. What effect could the presence of the pyridine on the palladium(II) have on the mechanism of this process? Looking at Scheme IV.3, the decrease in % ee indicates that two competing mechanisms going through the two different modes of hydroxypalladation could be in operation. First the pyridine ligand is neutral and less labile than the neighbouring

Scheme IV.3



chlorides. Thus the π-complex, **11**, will have to be neutral, the result being a net decrease in overall charge. At low chloride concentration different modes of hydroxypalladation are in operation. First the pyridine ligand is neutral and less labile than the neighbouring chlorides. At high concentrations of chloride ions, this makes it less likely for a second chloride to be lost creating a labile coordination site occupied by a water molecule. This is unlikely as it would result in a positively charged species, in the presence of acid medium. Thus **11** would not be expected to go on to form **12** except in the presence of concentrations of chloride as low as 0.05 M. Hence at chloride concentrations as low as 0.05 M, **12** could proceed to oxidation products via the path of cis oxypalladation as proposed by Henry,[86b] and an inversion of configuration during chirality transfer is obtained.

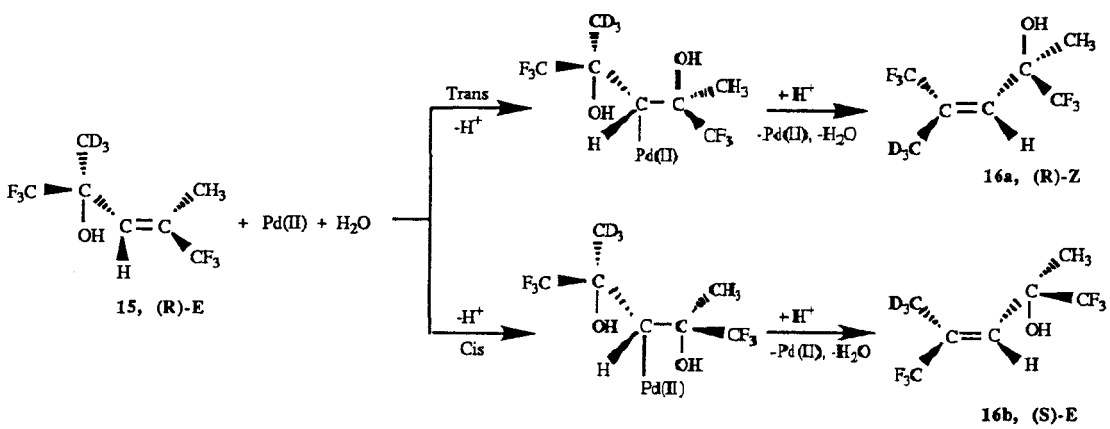
On the other hand the second mechanism, which is the minor reaction could proceed via the intermediate **13**, the σ-hydroxypalladation intermediate. **13** is formed from the external attack of a water molecule onto **11**. For oxidation to occur **13**

must lose a chloride resulting in the creation of the labile site which has previously been shown to be necessary for oxidative decomposition to occur to give carbonyl products. The configuration of this product would be expected to give a retention of configuration following chirality transfer.

At concentrations of chloride ions greater than 0.2 M isomerization is a possible route to give **14**. Very small quantities of the isomerized product, **14**, was detected and so it can be concluded that the kinetic product dominates under these reaction conditions with this substrate.

Scheme IV.4 outlines the products arising from the two possible modes of addition on the substrate given in Table IV.7. For the runs with $PdCl_4^{2-}$ at chloride

Scheme IV.4



concentrations, given in Table IV.7, equal to 0.1 M the process of isomerization is occurring by a mechanism which has an equilibrium proton loss followed by *cis*-hydroxypalladation which yields a product of inverted configuration. Thus a starting alcohol of R configuration, **15**, gives an alcohol of S configuration, **16b**, and the

opposite occurs for the starting alcohol having an S configuration.

At much higher concentrations of chloride, approximately 2.0 M, retention of configuration is obtained upon isomerization. This means that the only valid mechanism capable of giving a retention of configuration is a mechanism involving *trans*-hydroxypalladation similar to the one proposed by Bäckvall.[101] Thus **15** which has a (R)- configuration gives **16a**, which is also (R)-. By the principle of microscopic reversibility if hydroxypalladation is trans then dehydroxypalladation should also be trans. This accounts for the results at high chloride where **15-(R)-(E)** gives a product which is the opposite geometric isomer, **16a-(R)-(Z)**, but only in small amounts, accompanied by the starting allylic alcohol. The same is true for the starting alcohol **15-(S)-(E)**.

At chloride concentrations of 0.05 M and with $PdCl_3Py^-$ as the catalyst a unique result is obtained (see Table IV.7). Here the % inversion is much less than the % isomerization. This indicates that two competing reactions are active which are racemizing the product. It is fitting to mention that a similar result was obtained for the oxidation studies of 2-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol and discussed on page 101. The two competing reactions for the isomerization scheme are also similar to those for the oxidation results. Hence a mixture of (R)-enantiomer, **16a**, and the (S)- enantiomer, **16b**, are being produced from the (R)-starting alcohol, **15**. This reflects the suggestion earlier that both the *cis* and the *trans* mechanisms for isomerization are active under these conditions.

At higher chloride concentrations of 0.2 M, a retention of configuration is observed indicating that the *trans* mechanism is the one in operation. Thus **15**, the R enantiomer isomerizes to **16a**, the (R)- product.

The results of the isomerization studies of 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol, gives further support to the present argument that two

different mechanisms are operative for the oxypalladation process, and that the mechanism most active is influenced greatly by the catalyst as well as the reaction conditions.

D. Experiment

Materials; The Palladous Chloride was purchased from AESAR. 1,1,1-Trifluoro acetone (97%), Eu(III)$(fod)_3$, ethene, and LiCl were purchased from Aldrich Chemical Co.

Physical Measurements; All ^1H, ^2H, ^{13}C, and ^{19}F NMRs were recorded on a Varian VXR 300 NMR spectrometer. IRs were done on a Perkin Elmer 1310 Infrared Spectrophotometer. GCs were done on a Perkin Elmer Sigma 3B gas chromatograph. Potential output was read on an Orion Research Microprocessor pH/millivolt meter 811, and plots recorded on a Linear Instruments strip chart recorder. Optical rotations were measured with a Perkin Elmer 241 Polarimeter at 22°C.

Preparation of potassium trichloropyridine palladate(II), $KPdCl_3Py$.[162] The preparation was achieved following the procedure outlined in the experimental of Chapter III.

Preparation of 2,4-DNP stock solution.[168] 3 g of 2,4-DNP was dissolved in 15 mL of concentrated sulfuric acid, and stirred for 30 minutes. Carefully and slowly a solution of 20 mL water and 70 mL of 95 % ethanol was added. A dark red solution resulted. It was cooled, filtered, and stored in a dark bottle for further use.

Standardization of palladium(II) stock solutions.[168] The stock solutions were standardized gravimetrically with dimethylglyoxime in a manner similar to that described in the experimental of Chapter II.[150]

Oxidation products. Oxidations were carried out in deionized water at 25 °C on a 100 mL basis with the under the following conditions; $[Cl^-]$ = 0.15 M, $[H^+]$ = 0.15 M, [Pd(II)] = 0.13 M, and 0.1 M quinone was added daily in the solid form to reoxidize any palladium(0) formed. The initial allyl alcohol concentration was 0.10 M. Runs were kept stirred for over one week to accumulate enough product for analysis. The mixture was worked up by extraction in ethyl ether, drying with anhydrous

$MgSO_4$ and the MTPA derivative prepared. Final determination was done by GC and compared with the GC's of authentic MTPA derivatives.

Kinetic Studies. The reactions were run in the presence of p-benzoquinone (Q) which oxidized the Pd(0) formed in the oxidation back to Pd(II). The benzoquinone is reduced to hydroquinone (Q_H) in the process. The extent of reaction was determined by measuring the emf of the cell: Pt./ Q, QH_2, Pd(II), HCl, $LiClO_4$, allyl alcohol/ Pd(II), HCl, $LiClO_4$, QH_2/ Pt.[170] In the reference cell [quinone], q = [hydroquinone] = 0.005 M. The working cell had [quinone], q = 0.0095 M, [hydroquinone] = 0.0005 M, and [allylic alcohol] = .0.0045 M. From this the starting potential was calculated to be 37.8 mV and at the end of complete oxidation 0 mV, using the Nernst equation, $E = E^0 - (RT/nF)(\ln[q_h]/[q])$. When $[q] = [q_h]$ in the reference cell, then $E^0 = 0$ and the equation becomes $E = -(RT/nF)(\ln[q_h]/[q]) = 2.303(RT/nF)(\log[q]/[q_h]) = 29.57\log[q]/[q_h]$. E is measured in mV. In each compartment concentrations of the following were varied in the following ranges, and the ionic strength adjusted to 2.0 M with $LiClO_4$;

$[Cl^-]$ = 0.2 M to 1.0 M, (LiCl)

$[H^+]$ = 0.1 M to 0.5 M, ($HClO_4$)

[Pd(II)] = 0. 02 M to 0.20 M, (Li_2PdCl_4)

The apparatus and procedure are described in Figure IV.9. The entire setup of the electrochemical cell was immersed in a waterbath controlled by a thermostat at 25 °C. The results of these runs were converted by a basic program into time vs concentration, plotted as a first order in decrease of olefin concentration, and k_{obs}, $t_{1/2}$ and the order of reaction with respect to $[Cl^-]$, $[H^+]$, and [Pd(II)] determined.

Ethylene uptake experiment.[86a,154] The creased flask technique was employed here. The reactions were run in a creased flask at 25 °C and a constant ethylene pressure of 1 atmosphere. The gas uptake was measured by means of gas burets

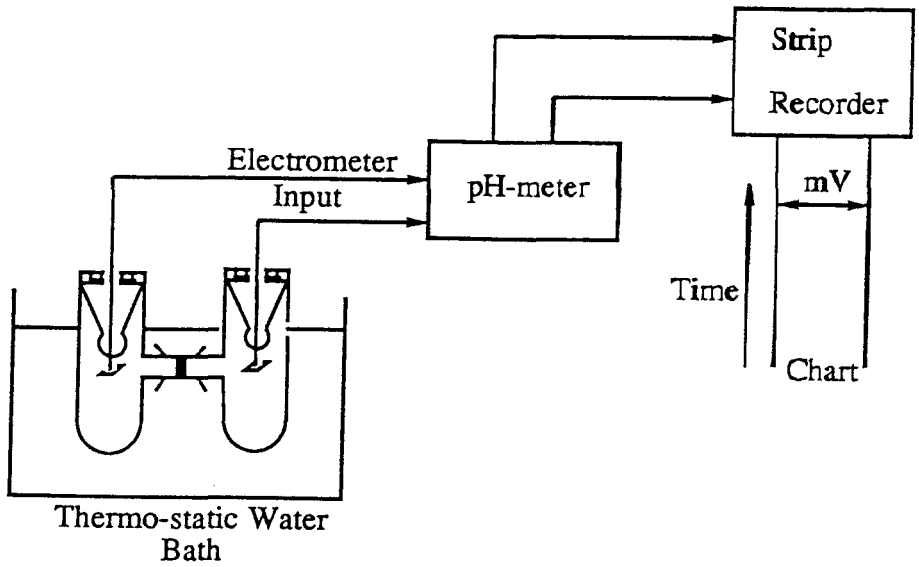


Figure IV.9. Potentiometer for the study of the oxidation kinetics using quinone/hydroquinone couple.

thermostated at the reaction temperature. The reaction flask was a 250 mL two necked coned shape flask with the sides indented, to increase stirring efficiency. A magnetic stirring bar was used for agitation. The apparatus is described and shown in Figure IV.10.

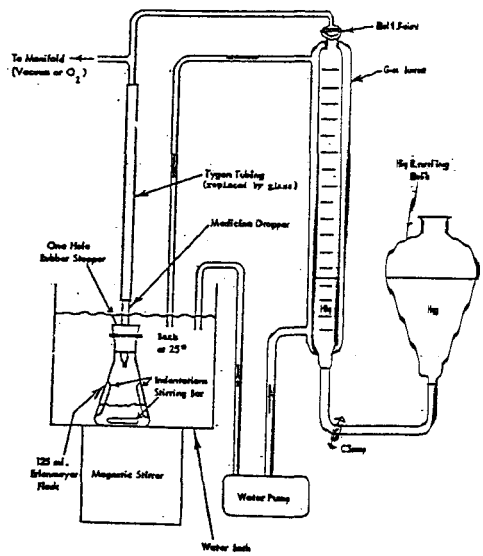


Figure IV.10. Gas uptake apparatus used for ethylene uptake studies.[5]

In a typical run the flask containing 50 mL of the reaction mixture was placed in a constant temperature bath and connected to the gas buret. The system was then evacuated for 10 minutes on the vacuum line with the stirrer running. The stirring was then stopped and the system pressurized to 1.0 atmosphere, with ethylene. The mercury in the gas buret and the leveling bulb were then equalized, and a reading taken. The stirrer was turned on to start the run. The pressure was kept constant by continuously leveling the mercury in the gas buret and bulb.

In all runs a plot of V_∞ - V vs time gave a straight line. The value of V_∞ was calculated from the solubility of ethylene in the reaction mixture plus the known concentration of $PdCl_4^{2-}$ stock solution which was analyzed by the dimethylglyoxime method. The value of V was corrected for a slow side reaction independent of palladous ion which consumed ethylene at a slow but constant rate. The rate of this reaction which was probably the hydration of ethylene to ethanol was determined by measuring the rate of ethylene uptake for several hours after the oxidation was completed. Solubilities were determined by measuring the ethylene uptake using solutions with the same composition as the reaction mixtures, but with the palladous ions omitted.

For the determination of the much faster initial ethylene uptake due to π-complex formation, the reaction mixture was stirred by a four blade stir bar to increase agitation. The volume of solution was increased to 100 mL. Runs were done over a 5 minute period, after which it was observed that plots of (V_∞ - V) vs time deviated from linearity.

The following equation was assumed in calculating the equilibrium constant K_1.

$$K_1 = [PdCl_2PyC_2H_4][Cl^-]/[PdCl_3Py^-][C_2H_4]$$

The net ethylene uptake was converted to moles of complex and this was subtracted from total palladous ion concentration to give $[PdCl_3Py^-]$. The value of $[Cl^-]$ was

then equal to; Total Chloride - 2[$PdCl_2PyC_2H_4$] - 3[$PdCl_3Py^-$].

The Preparation of 4-Hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone.[159] 1 gram atom of sodium pellets was washed twice with ether and covered with 200 mL of anhydrous ether. With vigorous stirring 60 g (1.3 moles) of absolute ethanol was added to the sodium during 30 minutes. To the well stirred solution of sodium ethoxide was added 100 g of 1,1,1-trifluoro acetone, the temperature of the solution being maintained below 0°C. After the solution had been stirred for 1 - 2 hours , it was poured into a mixture of 100 g sulfuric acid (98%), and 1000 g of ice. The solid hydrate was removed by filtration and the aqueous layer neutralized with NaOH solution, and extracted with ether. The solid hydrate was dissolved in ether, the ether layers combined and distilled to give a 69% yield of product. bp = 78 - 98°C. This crude product was distilled over P_2O_5 giving an overall yield of 65% of product which boiled at 82°C. 300 MHz ^1H NMR ($CDCl_3$): δ = 1.52 (s, 3H), 2.85 - 3.34 (q, 2H). ^{13}C ($CHCl_3$): 20, 40, 73, 78, 115, 125, 189. IR< (neat): 3500, 1770, 1200.

Preparation of (E)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one.[159] To 20 g of 4-hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone was added dropwise 10 mL of 20 % oleum. This mixture was refluxed for 6 hrs. and distilled giving 18 g (91%) of product boiling at 76°C. 300 MHz. ^1H NMR ($CDCl_3$): δ = 2.41 (s, 3H), 6.95 (s, 1H). ^{13}C ($CHCl_3$): 12, 115, 118, 122, 150, 180. IR, (neat): 3100, 1740, 1650, 1190.

Preparation of racemic-(E)-4-Methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol, (Luché reduction).[148] 4-Methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol and $CeCl_3.7H_2O$, (1 mmole) each, were dissolved in 2.5 mL of methanol. $NaBH_4$ (38 mg, 1 mmole) was added in one portion with stirring. H_2 gas evolved accompanied by a temperature rise, (approx. 35 -40°C). Stirring was continued for 3 - 5 min. before the pH was adjusted to neutrality with dilute aqueous HCl. The mixture was extracted (ether), dried ($MgSO_4$), and the solvent evaporated. The crude residue was distilled over

P_2O_5 yielding 91% of product, bp 118 - 122°C.

Preparation of (-)-(R)-(E)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol (enantioselective reduction).[166] To 69 mL of 0.88 M $LiAlH_4$ (0.06 moles) in anhydrous ether was added dropwise over 1 hr. 10.74 g (0.06 moles) of (L)-N-methyl ephedrine, dissolved in 300 mL of anhydrous ether. It was set aside for 30 mins. at room temperature and 14.64 g (0.12 moles) of 3,5-dimethylphenol dissolved in 100 mL of anhydrous ether was added over 30 mins. This was allowed to stand for 2 hrs. at room temperature. The temperature was then lowered to -15°C and maintained for 1 hr. to equilibrate. 10.3 g (0.05 moles) of (E)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one dissolved in 30 mL of anhydrous ether, was introduced dropwise over 2 hrs. At the end of addition the mixture was kept at -15°C for an additional 1 hr. The mixture was hydrolyzed with NaOH. The organic phase was washed twice with 100 mL of 2 M HCl, followed with 100 mL of 2 M NaOH. All the aqueous phases were combined, neutralized, and extracted to recover 83.8% of the (L)-N-methyl ephedrine. The ether phase was dried ($MgSO_4$), and distilled to give 40% yield of the desired alcohol. bp = 118 - 122°C, (α^{22}_D = -2.06° ± 0.02°(c,2.0,$CHCl_3$), 18% ee). 300MHz ^1H NMR ($CDCl_3$): δ = 1.95 (s, 3H), 4.70 (quint, 1H), 6.10 (d, 1H). ^{13}C ($CHCl_3$): 12, 68, 123, 124, 125, 135. *Anal.* Calcd for $C_6H_6F_6O$: C, 33.63; H, 2.91. Found: C, 33.65; H, 2.70.

Preparation of (S)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetylchloride,[(+)-MTPA-Cl].[167] (R)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid ((R)-(+)-MTPA), 41 g, thionyl chloride, 75 mL (distilled practical grade) and sodium chloride, 0.5 g were refluxed together for 50 hrs. After excess thionyl chloride was removed by vacuum evaporation, the residue was distilled to give 43.8 g of (S)-(+)-MTPA-Cl, 90% yield. bp = 54 - 56°C (1mm), [α^{22}_D] = 128.7° ± 0.2°.

Preparation of the Ester of MTPA.[167] 4-Methyl-1,1,1,5,5,5-hexafluoro-3-penten-

2-ol, 0.3078 g (0.148 mmoles) and distilled (S)-(+)-MTPA-Cl, 0.0379g (0.15 mMoles) were mixed in CCl_4, 5 drops, and dry pyridine, 5 mL , and allowed to stand in a stoppered flask for 12 hrs. Water, 1 mL, was added and the reaction mixture transferred to a separatory funnel containing 20 mL ether. The ether solution, was washed successively with dilute HCl, saturated $NaHCO_3$, and water. It was then dried ($MgSO_4$), filtered, and vacuum evaporated. The residue was dissolved in $CDCl_3$ for NMR studies. 300 MHz ^1H NMR ($CDCl_3$): δ = 2.05 (m, 3H), 3.50 (m, 3H), 5.80 - 6.30 (m, 2H), 7.30 -7.70 (m, 5H). ^{13}C ($CHCl_3$): 11.7, 55.7, 67.6, 120, 124, 127, 127.2, 128.6, 130.1, 138.9, 165. IR, (neat): 3090, 2990, 2970, 2850, 1765, 1590, 1500, 1450, 1190, 1130, 770, 700. *Anal.* Calcd for $C_{16}H_{13}F_9O_3$: C, 45.30; H, 3.09. Found: C, 45.38; H, 3.08.

Preparation of esters of MTPA in gram quantities.[167] Esters were prepared as in the previous preparation, but in addition the reaction mixture was refluxed for 7 hrs. followed by standing for 12 hrs. After working up the product was distilled under reduced pressure to obtain pure products.

Separation and Resolution of the Diastereo Isomers of 4-Methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-yl-α-methoxy-α-trifluoromethyl-phenylacetate. The diastereomers were separately collected from a 20 ft. x 0.21 in. DCQF-1 column at 195°C, helium flow rate 60 ml/min. Injections of 0.5 mL were done for each run. Retention times were 174 and 180 mins for the respective diastereomers. Each diastereomer was reduced by lithium aluminum hydride (1 : 4, $LiAlH_4$: ester), in anhydrous ether. The ether phase was dried ($MgSO_4$), and distilled giving the pure enantiomer.

An Example of Assignment of Configuration by Shift studies.[167] NMR spectra of (R)-(+)-MTPA ester of the partially active 4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol ($[\alpha]^{22}_D$ = 5.81° ± 0.01° (c,2.0,$CHCl_3$), 50% ee) were taken with molar

ratio of $Eu(fod)_3$ to MTPA ester of 0.1-0.3 in $CDCL_3$, see Figure IV.11, and the

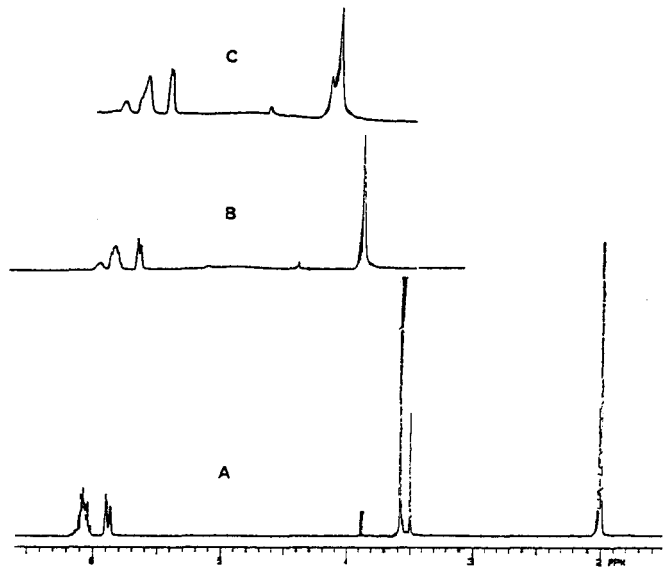


Figure IV.11. 300 MHz. ^1H NMR spectra of (R)-(+)-MTPA esters of (-)-(R)-E- and (+)-(S)-E-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol observing the OCH_3 resonance in $CDCl_4$ containing various molar ratios of $Eu(fod)_3$: A, 0 mol; B, 0.1 mol; C, 0.3 mol.

magnitudes of induced chemical shift of OMe signals were plotted vs molar ratio ($Eu(fod)_3$/MTPA ester). In this range the induced shifts were essentially linear with respect to molar ratios of reagent. The ratio of peak areas of well separated OMe signals with larger and smaller lanthanide induced shift (LIS) values was (25/75). Therefore (+)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol has (S)- configuration.

2,4-Dinitrophenylhydrazine of 4-hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone.[168] Crystalline derivatives were obtained by standard procedures. 300 MHz. ^1H NMR ($CDCl_3$): δ = 1.55 (s, 3H), 2.8-3.2 (q, 2H), 8.1 (d, 1H), 8.45 (d, 1H), 9.15 (s, 1H), 12.3 (s, 1H). ^{13}C ($CHCl_3$): 22, 32, 76, 118, 124, 126, 130, 132, 145.

5,7-Bis-(trifluoromethyl)-5-hydroxy-7-methyl-1,4-dioxacycloheptane. A mixture of 25 g (0.11 moles) of 4-hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone and 19.0 g (0.22 moles) of ethylene chlorohydrin was treated with 30.8 g (0.22 mole) of potassium carbonate added in portions over 1 hr. with stirring and external cooling.

The mixture was stirred at room temperature for 4 hrs. and poured into 150 mL of water. The organic phase was extracted with pentane and the pentane extracts dried ($MgSO_4$), concentrated, and distilled. 16 g of product was obtained. 300 MHz ^1H NMR ($CDCl_3$): δ = 1.4 (s, 3H), 2.1-2.4 (q, 2H), 3.8 (s,OH), 4.2 (s, 4H). ^{13}C ($CHCl_3$): 21, 34, 67, 74, 107, 124, 127. IR, (neat): 3500, 3000, 2910, 1180.

MTPA Ester for 4-Hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone. 1.3 mmoles (0.3328 g) of dried (S)-(+)-MTPA-Cl was added, under a flow of nitrogen to a mixture of 15 mL anhydrous pyridine and 1.0 mmoles (0.225 g) of 4-hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone. This was refluxed for 2 hours, followed by standing at room temperature for and additional 10 hours. There was a yellow crystalline precipitate accompanied by darkening of the solution. Excess 3,3-dimethylamino-1-propylamine, and 5.0 mL of CCl_4 were added and the solution stirred for 5 minutes. It was then washed with 20 % HCL solution, then saturated Na_2CO_3 and saturated NaCl., dried with anhydrous $MgSO_4$ and the solvent evaporated. 300 MHz. ^1H NMR ($CDCl_3$): δ = 1.25 - 1.50 (m, 3H), 3.55 - 3.80 (m, 3H), 5.80 - 6.10 (m, 1H), 6.30 - 6.60 (m, 1H), 7.30 - 7.90 (m, 5H).

Separation and Resolution of the Diastereo Isomers of 4-Methyl-1,1,1,5,5,5-hexafluoro-2-pentanone-4-yl-α-methoxy-α-trifluoromethyl-phenylacetate. The diastereomers were collected separately from a 20 ft x 0.21 in. DCQF-1 column at 170 °C. Injections of 0.50 mL were done for each run. Retention times were 69 and 87 mins. for the respective diastereomers. These enantiomers were reduced using lithium aluminum hydride in the usual manner. The first diastereomer collected had ee = 100% using ^1H NMR and Eu(III)FOD shift studies of the OCH_3 resonance occurring at 3.35 ppm. Upon reduction to the alcohol optical measurements yielded $[\alpha]^{22}_{Dmax}$ = -8.2° ± 0.2°(c, 1.0, $CHCl_3$). Lanthanide induced shift studies indicated this to be the (S)-(+)- enantiomer. The second diastereomer with retention time 87

mins. was obtained in 36 % ee. After hydrolysis of the ester, the alcohol gave $[\alpha]^{22}_{D}$ = 3.16 ° ± 0.20 °(c,2.0, $CHCl_3$). $[\alpha]^{22D}_{max}$ = -8.78 ° ± 0.1 °.

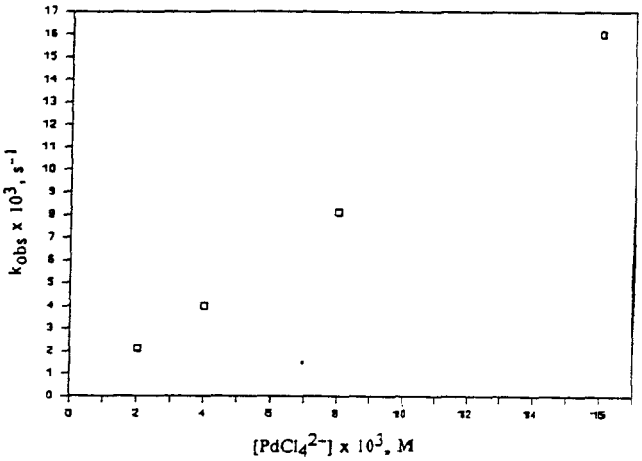
Preparation and Resolution of E-2-Methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-yl-α-methoxy-α-(trifluoromethyl)-phenylacetate. The ester was synthesised in the usual way except that it was left at reflux for 12 hr. Upon workup the following data were compiled. 300 MHz. ^1H NMR ($CDCl_3$): δ = 2.13 (s, 3H), 3.45 (m, 3H), 7.3 - 7.7 (m, 5H). ^{13}C ($CDCl_3$): 16, 33, 53, 56, 74, 85, 96, 123, 126, 127, 128, 130, 131, 133, 161.

The diastereomers were separated by GC using a 20 ft. x 0.21 in. DCQF-1 column at 185 °C, and flow rate of 60 mL/min. Retention times were 114 min. for the RS diastereomer, and 138 min. for the RR diastereomer. Eu(fod)$_3$ shift studies were done in the usual manner and subsequent hyrdrolysis with $LiAlH_4$ revealed that (-)-(R)-(E) had $[\alpha^{22}_{D}]_{max}$ = -9.3° ± 0.3° (c,2.0, $CHCl_3$), and (+)-(S)-(E) had $[\alpha^{22}_{D}]_{max}$ = +9.5° ± 0.1° (c,2.0, $CHCl_3$).

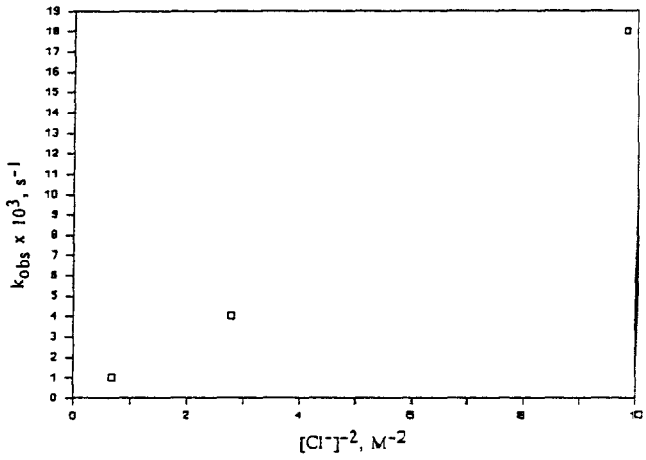
Preparation and Resolution of Z-2,4-Dimethyl-1,1,1,5,5,5-hexafluoro-3-penten-2-yl-α-methoxy-α-(trifluoromethyl)-phenylacetate. The alcohol, 2,4-dimethyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol was prepared in the usual manner by grignard reaction of CH_3MgI with Z-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one. 300 MHz ^1H NMR ($CDCl_3$): δ = 1.55 (3H), 2.1 (s, 3H), 2,7 (OH), 6.15 (s, 1H). ^{13}C ($CDCl_3$): 11, 15, 20, 74, 118, 121, 128.5, 132.

The MTPA diastereomers were synthesised by standard procedure. 300 MHz, ^1H NMR ($CDCl_3$): δ = 1.5 - 1.7 (3H), 2.1 (s, 3H), 3.7 (s, 3H), 5.9 - 6.3 (1H), 7.4 - 7.8 (m, 5H). ^{13}C ($CDCl_3$): 16.5, 20, 22, 50, 56, 70, 116, 122, 125, 128, 129, 130, 132, 140. LIS studies were done with Eu(fod)$_3$ and results indicated that the RR diastereomer had retetention a time of 38 min., and the RS 43.5 min. This was collected from a 20 ft. x 0.21 in. DCQF-1 column at 190 °C, helium flow rate 60 mL/min.

APPENDIX A



A.



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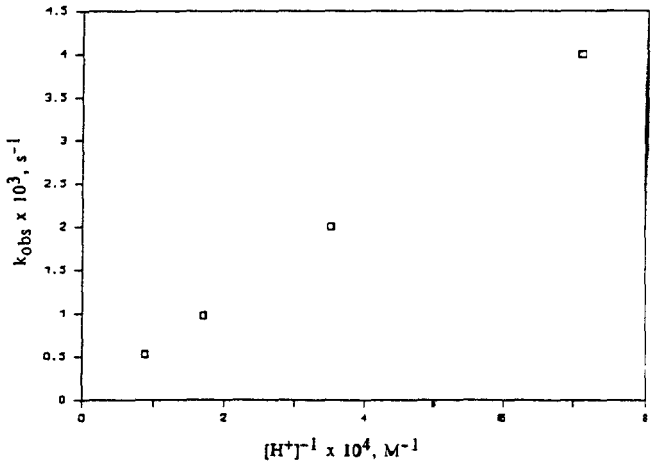
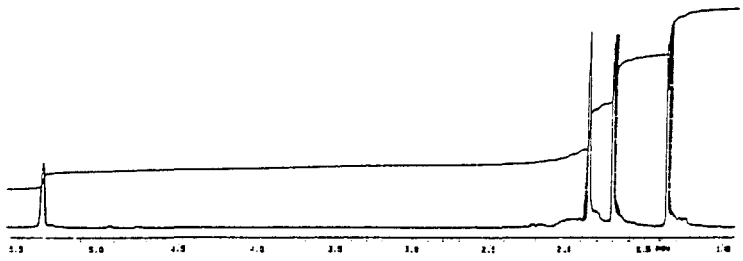
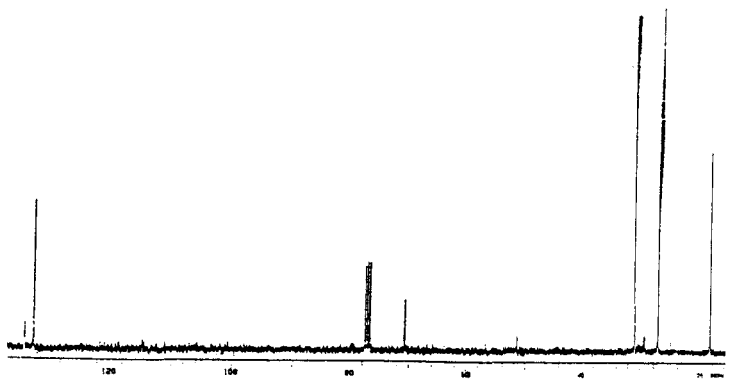


C.

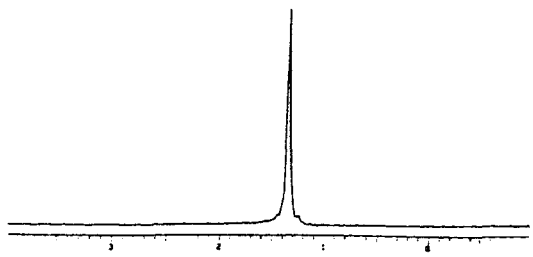
A.1. Representative plots taken from Table II.1 showing the order of dependence of the rate of reaction on: A. palladium(II) concentration; B. chloride concentration and C. acid concentration.



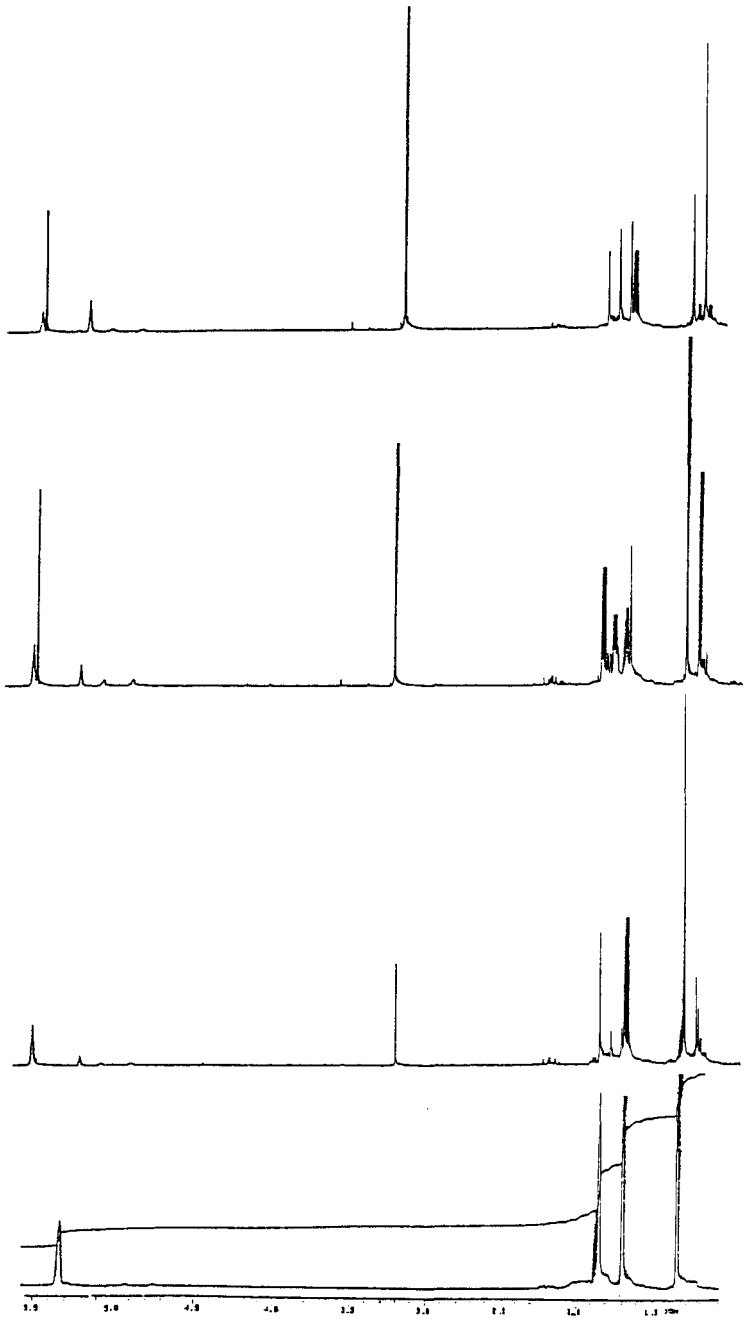
A.2. ^{1}H NMR of 2-methyl-d_3-4-methyl-3-penten-2-ol.



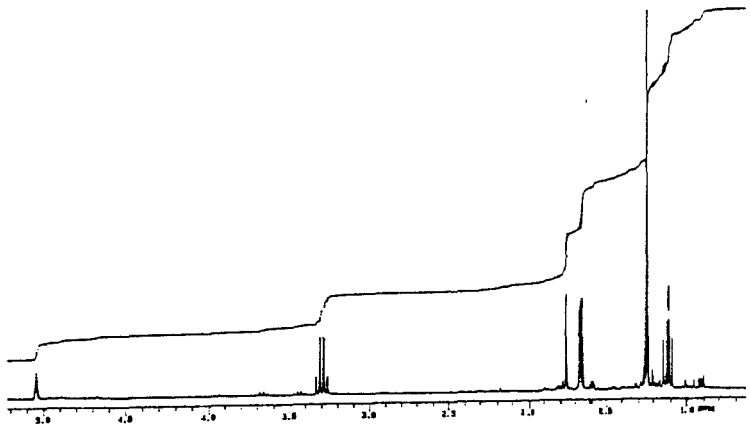
A.3. ^{13}C NMR of 2-methyl-d_3-4-methyl-3-penten-2-ol.



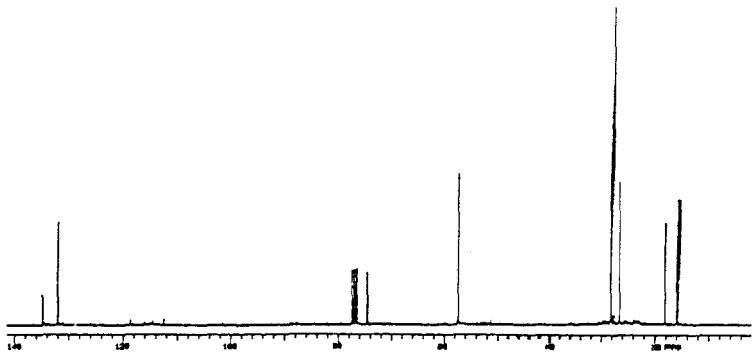
A.4. ^{2}H NMR of 2-methyl-d_3-4-methyl-3-penten-2-ol.



A.5. ^{1}H NMR of the progressive transformation of 2-methyl-d_3-4-methyl-3-penten-2-ol to 2-methoxy-2-methyl-4-methyl-d_3-3-pentene in methanol catalyzed by $PdCl_4^{2-}$.

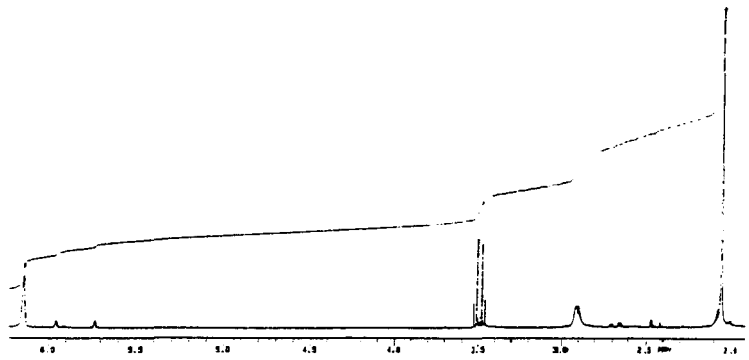


A.6. ^{1}H NMR of 2-ethoxy-2,4-dimethyl-3-penten-2-ol.

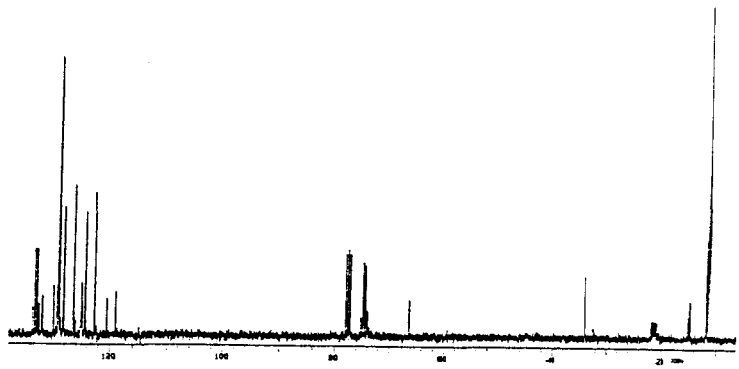


A.7. ^{13}C NMR of 2-ethoxy-2,4-dimethyl-3-penten-2-ol.

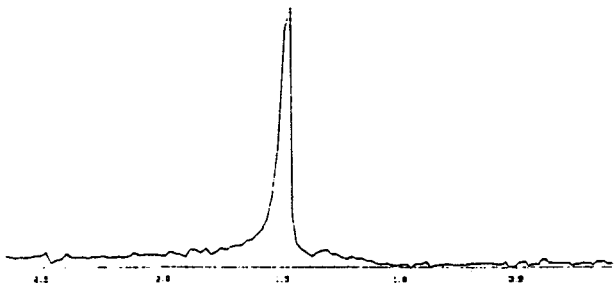
APPENDIX B



B.1. ^{1}H NMR of 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol.

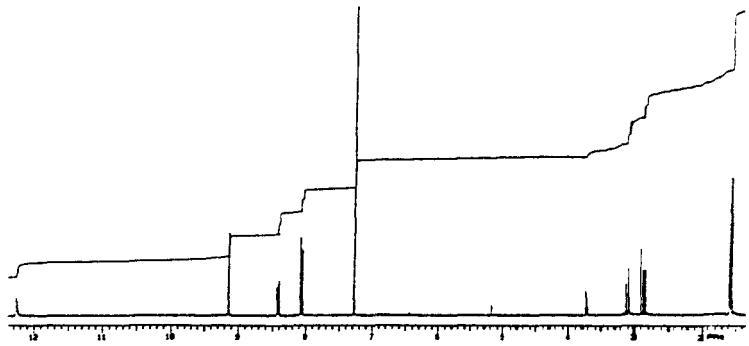


B.2. ^{13}C NMR of 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol.

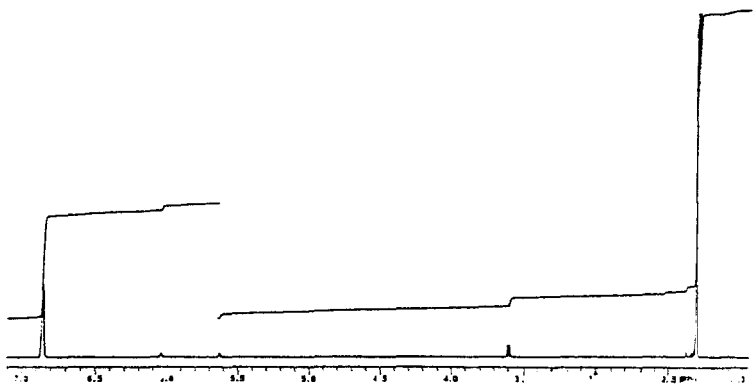


B.3. ^{2}H NMR of 2-methyl-d_3-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol.

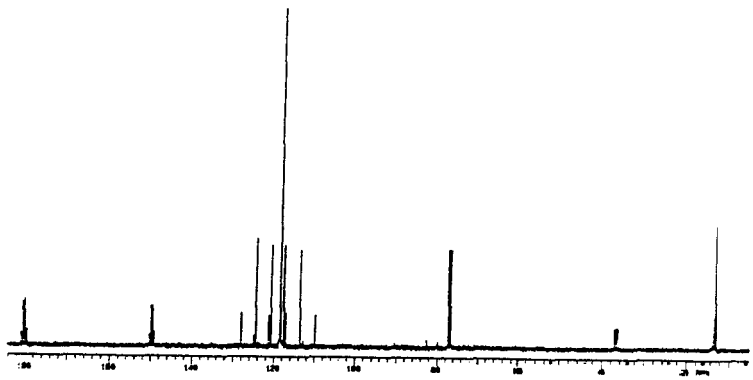
APPENDIX C



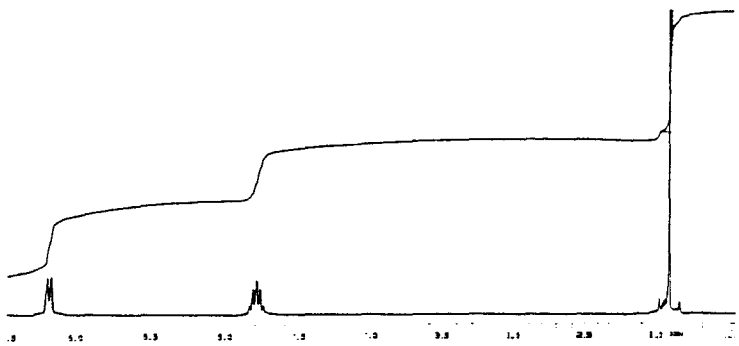
C.1. ^{1}H NMR of the 2,4-DNP derivative of 4-hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one.



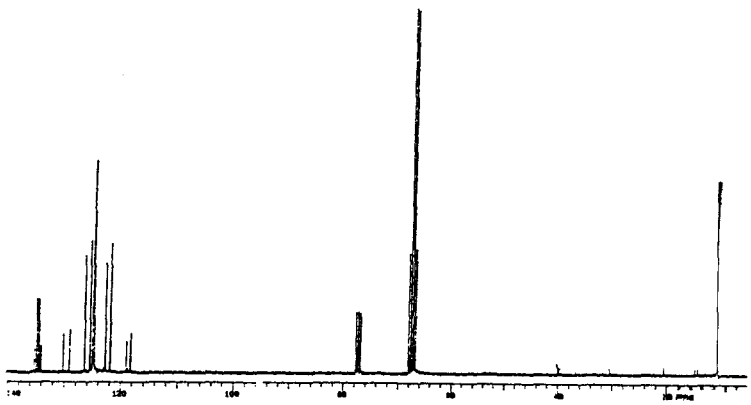
C.2. ^{1}H NMR of (E)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one.



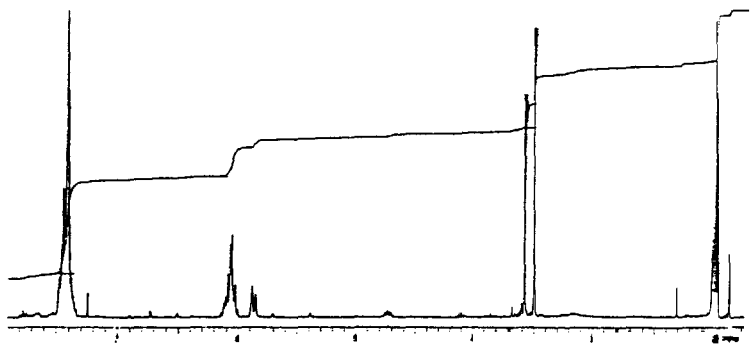
C.3. ^{13}C NMR of (E)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one.



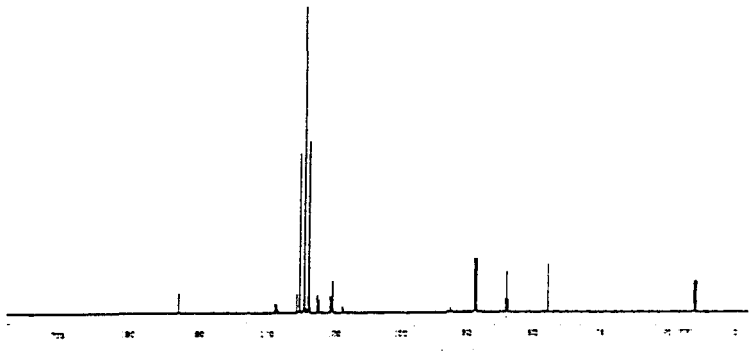
C.4. ^{1}H NMR of 4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol.



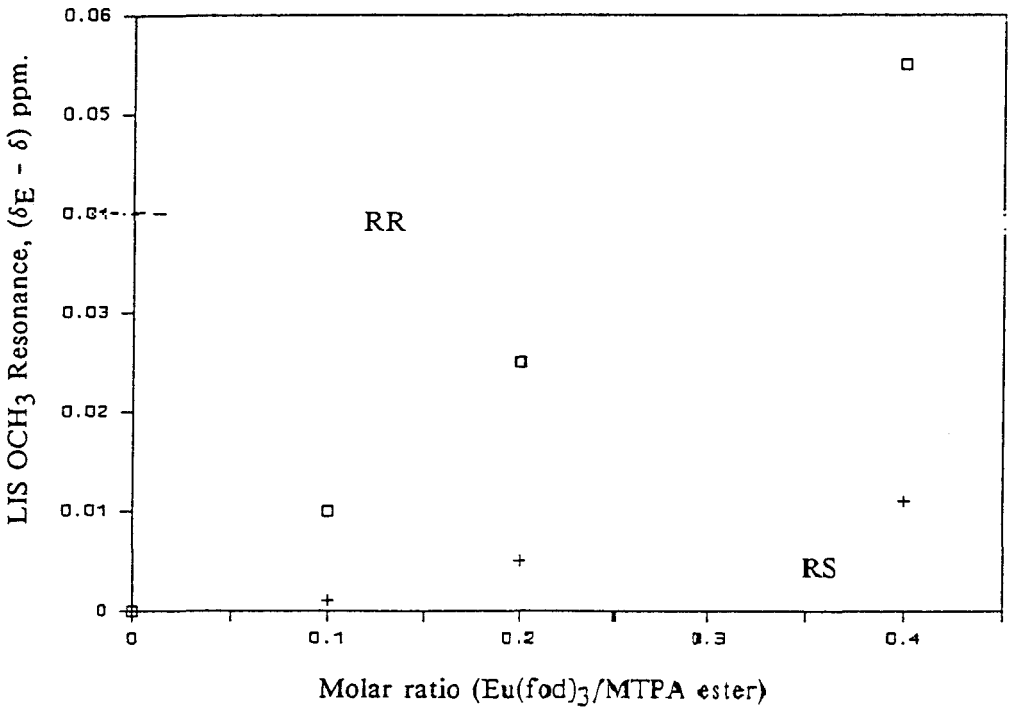
C.5. ^{13}C NMR of 2-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol.



C.6. ^{1}H NMR of a mixture of RR and RS diastereomers of 2-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-yl-α-methoxy-α-(trifluoromethyl)-phenylacetate.



C.7. ^{13}C NMR of RR-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-yl-α-methoxy-α-(trifluoromethyl)-phenylacetate.



C.8. Representative plots of the lanthanide induced shift (LIS), of the methoxy proton resonance vs. molar ratios of $Eu(fod)_3$ for the diastereomeric esters of 4-hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone.

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VITA

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